CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215383Orig1s000

OTHER REVIEW(S)

M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM:	Gautam Mehta, Clinical Reviewer, Division of Oncology 2 (DO2)
THROUGH:	Amy Barone, Acting Team Leader, DO2
THROUGH:	Harpreet Singh, Division Director, DO2
SUBMISSION #:	NDA 215383
REQUESTED BY:	CDER/DO1
PRODUCT:	Belzutifan
SPONSOR:	Merck
DATE OF REQUEST:	December 22, 2020

I. Executive Summary

Belzutifan (NDA 215383) is a first-in-class inhibitor of HIF2 alpha and new molecular entity; the application, which participated in the Real Time Oncology Review (RTOR) program is currently under review in Division of Oncology 1 (DO1). The proposed indication is “treatment of patients with von Hippel-Lindau disease (VHL)-associated renal cell carcinoma (RCC)”. There are no currently-approved drugs for the proposed indication, or other VHL-associated tumors. On December 22, 2020, DO1 requested a consult from DO2, with the following specific request:

“Assess the safety and efficacy of this drug in comparison with currently available treatment options for these non-RCC tumors (central nervous system [CNS] hemangioblastomas and pancreatic neuroendocrine tumors [pNETs]), especially regarding including some of these data in product labeling.”

The Applicant submitted single-arm data from a single study in 61 patients with VHL and RCC treated with belzutifan, which included tumor response data from 24 patients with measurable CNS hemangioblastomas and 12 patients with pNETs. Given the high rates of objective responses in these tumor types and the totality of evidence of efficacy across multiple tumor types with similar pathogenesis, these data support inclusion of CNS hemangioblastomas and pNETs in the indication statement and Section 14 of the label. Labeling negotiations are ongoing, see label for finalized language

II. Study Background and Proposed Labeling

Belzutifan was investigated in Study-004 (NCT03401788), an open-label Phase 2 clinical trial in 61 patients with VHL disease who had at least one measurable

renal cell carcinoma tumor (as defined by RECIST v1.1) localized to the kidney. Patients received belzutifan 120 mg once daily until progression of disease or unacceptable toxicity. Patients were evaluated radiologically every 12 weeks. The study excluded patients who had any evidence of metastatic disease, an immediate need for surgical intervention for tumor treatment, any major surgical procedure completed within 4 weeks prior to study enrollment, any major cardiovascular event within 6 months prior to study drug administration, or prior systemic treatments for VHL disease-associated RCC.

Patients in the study population had a median age of 41 years, were 52.5% male and 90.2% White. Seventy-seven percent of patients had prior RCC surgical procedures. According to the Applicant's initial submission, fifty patients (82%) harbored CNS hemangioblastomas and 20 patients (20%) harbored pancreatic neuroendocrine tumors, based on agreement by at least two readers on central independent review committee (IRC).

The major efficacy endpoint for the treatment of VHL disease-associated RCC was overall response rate (ORR) using RECIST v1.1 as assessed by IRC. Additional efficacy endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), time to response (TTR), and time to surgery (TTS).

The Applicant has proposed an indication for belzutifan as the treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery. The Applicant also including the following table in Section 14 of the draft label describing clinical efficacy among VHL-associated CNS hemangioblastomas and pNETs:

(b) (4)

[redacted]

III. CNS Hemangioblastomas

A) Background:

CNS hemangioblastomas occur in 60-80% of patients with VHL and are the most common VHL-related cause of mortality among the subset of patients who harbor these tumors.(Lonser 2014) Hemangioblastomas in VHL typically arise in the cerebellum, brainstem, and spinal cord. Approximately 10% of tumors are associated with cysts or spinal syringes, however cysts are associated with the majority of symptom-producing tumors.(Lonser 2014) A prospective natural history study of 250 patients with VHL has demonstrated that the majority of CNS hemangioblastomas (72%) grow in a saltatory fashion characterized by periods of quiescence that can average over 2 years in duration.(Lonser 2014, Ammerman 2006) These tumors are not known to spontaneously regress.

The standard of care for VHL-associated CNS hemangioblastomas is surgical resection, which leads to stable or improved neurologic function in the majority of patients (96%).(Mehta 2010, Wind 2010, Jagannathan 2008) A prospective study

of stereotactic radiosurgery for CNS hemangioblastomas demonstrated regression among 31% of tumors by volumetric analysis.(Asthagiri 2010) More recent multi-center, retrospective analysis described tumor regression in 40% of tumors, with response associated with smaller tumor size.(Kano, 2015) Stereotactic radiosurgery was well-tolerated in these studies. To date, no effective medical therapies have been identified for hemangioblastomas. A single-arm study of the tyrosine kinase inhibitor, pazopanib, in patients with VHL resulted in 2 partial responses among 49 hemangioblastomas (4%).(Jonasch 2018) Tumor response to pazopanib appears to be lesion-specific, with variable responses reported in individual patients with multiple hemangioblastomas.(Taylor 2018)

Because of the unpredictable nature of tumor growth, management of VHL-associated hemangioblastomas is typically based on clinical signs and symptoms. This management paradigm is based largely on 10-year prospective natural history from 19 patients with VHL-associated hemangioblastomas reported by Ammerman and colleagues.(Ammerman 2006) Because of the saltatory growth pattern of tumors, they reported that if the decision to treat were based on radiographic progression alone, each patient in the study would have undergone approximately 4 additional procedures during the study period. Furthermore, the authors found that 45% of hemangioblastomas that eventually produced symptoms were not among the tumors apparent on the initial MRI.

B) Data to support labeling:

Fifty patients in Study-004 were found to have CNS hemangioblastomas at baseline. IRC assessment was limited to patients who were initially assessed as having CNS lesions at screening and underwent serial MRI assessments. Solid tumors and cysts were measured together in IRC assessments per RECIST v1.1 in the initial submission. Review of the CNS procedures document from the independent radiology review vendor, (b) (4), revealed the following rationale (Section 7.4.2):

“maximum diameter of the lesion should be recorded including the enhancing solid component and/or the cystic component as the cystic component is thought to be a part of the tumor.”

Cysts associated with CNS hemangioblastomas are generally peri-tumoral and not intra-tumoral.1,2 In a natural history study of 250 patients with VHL harboring 2505 CNS hemangioblastomas, 247 tumors (10%) developed peri-tumoral cysts whereas only 37 (1.5%) developed intra-tumoral cysts.(Lonser 2014) As such, CNS hemangioblastoma-associated cysts are generally not considered to be neoplastic.(Mehta 2010, Jagannathan 2008)

Further review of the CNS procedures document (Section 7.4.2) and images provided in Merck response to information request dated May 21, 2021 suggested that IRC review included brain and spine edema in tumor volume.

"Target lesions should be measured on the T1W images post gadolinium to include the enhancing component with reference to, and in concert with, the findings on the T2/FLAIR images to define the borders of the cystic components that should be included in the measurements."

Tumors with intra-tumoral cysts should be measured using post-contrast T1-weighted imaging to measure the diameter of the enhancing tumor that surrounds the intra-tumoral cyst.(Lonser 2014, Jagannathan 2008) Fluid-attenuated inversion recovery (FLAIR) imaging in particular should be reserved for measuring edema and does not identify free fluid that is found in either intra-tumoral or peri-tumoral cysts.(Husstedt 2000, Tsuchiya 1996)

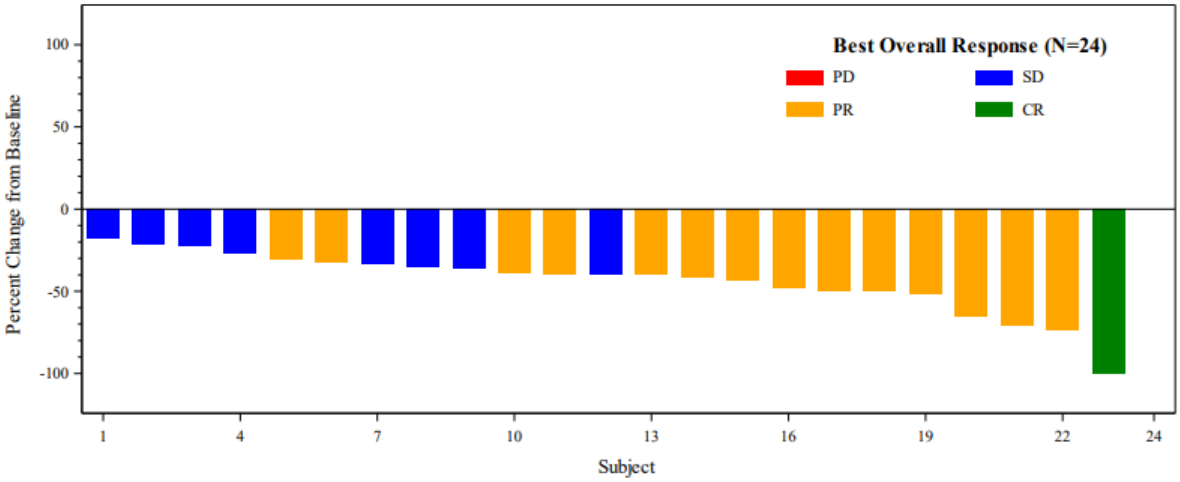
Based on the above considerations, we requested that the Applicant provide a re-review of the CNS hemangioblastoma imaging data with the following changes:

1) Define maximal tumor diameter as the maximal contrast-enhancing diameter measured using post-contrast T1-weighted MRI. Do not include peri-tumoral cyst diameter in tumor measurements.

2) Include patients with measurable disease at baseline only.

The Applicant provided a fresh re-review of the CNS imaging data on July 8, 2021, identifying 24 patients with measurable disease at baseline. Among these, 23 patients had post-baseline measurements, all of whom experienced a net reduction in the sum diameters of CNS hemangioblastomas.

Figure 1
Waterfall Plot - Percentage Change in Total Sum of CNS Hemangioblastoma Target Lesions Diameters from Baseline to Post-Baseline Maximum % Reduction (RECIST 1.1) – IRC
Efficacy Analysis Set - Patients with Evaluable CNS Hemangioblastoma Tumors at Baseline

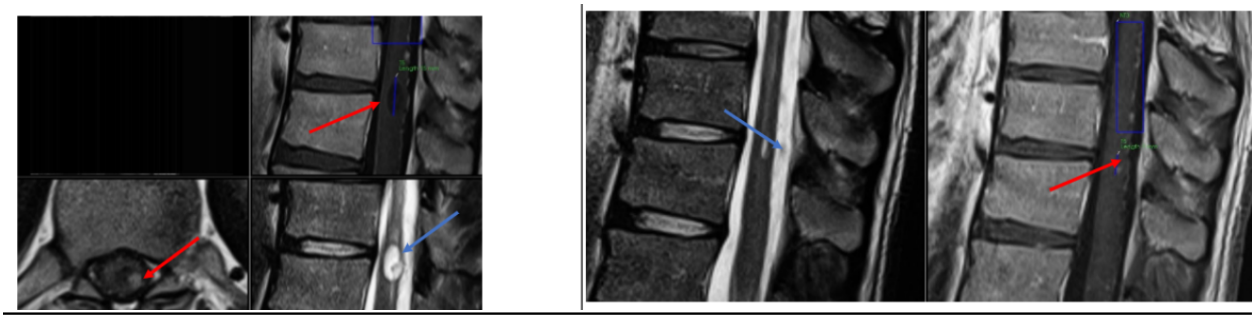


Subjects without either post-baseline evaluable lesion measurements or target lesions or with all post-baseline non-evaluable time-point responses appear as blank on the right of the figure.
Number (%) of patients with maximum % reduction in sum of diameters of target lesions < 0 = 23 (95.8)
CNS hemangioblastoma (HB) assessments followed RECIST 1.1 criteria; tumor measurement included only HB, not HB-associated cyst. Patients with measurable CNS HB at baseline were included in analysis.
Date of Data Cut-off: 01DEC2020

Source: [P004V01MK6482: adam-adeff]

According to IRC assessment per RECIST v1.1, the confirmed ORR was 62.5% (95% CI: 40.6, 81.2). There was 1 complete response (CR) and 14 partial responses (PR). All 11 evaluable patients had ongoing responses at 1 year. The median duration of response (DOR) was not evaluable, however the mean DOR was 63.4 weeks. The median time to response was 3.1 months (range 2.4 to 11.0 months). There were 8 patients with stable disease and no patients with disease progression.

Data on individual cyst responses are not available, however the Sponsor shared radiologic images of 5 tumor-associated cysts that decreased in size during the study period as examples (thoracic spinal cord hemangioblastoma shown before and after belzutifan)



Data on neurologic signs or symptoms in the treatment population were not available. One patient underwent surgery for a progressive CNS

hemangioblastoma (non-measurable) and 1 patient underwent stereotactic radiosurgery for 5 non-measurable, asymptomatic, non-growing hemangioblastomas before the first study imaging assessment.

C) DO2 Recommendations:
DO2 recommends including VHL-associated CNS hemangioblastomas in the indication statement or Section 14 of the beltuzifan label for the following reasons:

1) Indication statement: IRC analyses of VHL-associated CNS hemangioblastomas demonstrated objective responses in the solid tumor component of 15 of 24 patients with measurable lesions. Natural history data demonstrates that CNS hemangioblastomas do not spontaneously regress, therefore these data suggest a biologic response to therapy. Responses were also observed in tumor-associated cysts and syringes, which are frequent causes of morbidity with CNS hemangioblastomas. Given the observed responses to belzutifan in other tumor types and the shared pathogenic mechanisms in these tumors in VHL, the totality of evidence supports inclusion of CNS hemangioblastomas in the indication statement. Given the median time to response of 3.1 months, this therapy is not appropriate for patients who require urgent intervention. We recommend the following indication statement:

   Belzutifan is indicated for adult patients with VHL disease who require non-urgent treatment for CNS hemangioblastomas and who elect not to undergo surgery or for whom surgery is not considered appropriate.

2) Section 14: We recommend inclusion of ORR data in the table below:

	TRADEMARK 120 mg daily N=61	
Endpoint	**Patients with Evaluable PNET n=12**	**Patients with Evaluable CNS Hemangioblastomas n=24**
Duration of follow up Median in months (range)	22.2 (20.3, 25.8)	21.9 (4.2, 30.1)
Overall Response Rate		
ORR* (95% CI)	83.3% (n=10) (51.6%, 97.9%)	62.5%, n=15 (40.6%, 81.2%)
Complete response	16.7% (2)	4.2% (1)
Partial response	66.7% (8)	58.3% (14)
Duration of Response‡		
Median in months (range)	Not reached (10.8+, 19.4+)	Not reached (3.7+, 22.2+)
% (n) with duration ≥ 12 months	50.0% (5)	73.3% (11)
Time to Response		
Median in months (range)	8.1 (2.7, 11.0)	3.1 (2.5, 11.0)

Additionally, we recommend inclusion of the following information in Section 14 to capture that responses were noted CNS hemangioblastomas cysts and syringes and that neurologic function was not assessed in Study 004:

Radiologic responses were also seen in CNS hemangioblastoma-associated cysts and syringes.
Neurologic function in patients with CNS hemangioblastomas was not assessed.

IV. Pancreatic neuroendocrine tumors

A) Background:

Pancreatic neuroendocrine tumors (pNETs) occur in 8-17% of patients with VHL with a median age at onset of 34 years (range 14-55 years).(Blansfield 2007, Igarashi 2014, Tirosh 2018, Krauss 2018) Pancreatic NETs in VHL are rarely functional (<1%), but metastasize in 7.5-20% of patients.(Blansfield 2007, Krauss 2018, Igarashi 2014) Analysis of the Surveillance, Epidemiology, and End Results (SEER) database found no increase in all-cause mortality in patients with pNET (HR 0.42, 95% CI 0.12-1.5, p=0.18), although there was an increased risk in patients with metastatic pNET (HR 3.71, 95% CI 1.4-9.8, p=0.008).(Arnon, VHL Research Symposium 2020) Eighty-seven patients with VHL-associated pNETs (163 tumors) were followed in a prospective natural history study.(Weisbrod 2014) Approximately 20% of the differences between consecutive measurements were radiographic decreases in size and 20% were no change. Two of 4 malignant pNETs in this cohort had a net decrease in size over time.

The standard of care for VHL-associated pNETs is surgical resection. It is recommended that pNETs ≥3 cm in diameter that are located in the body or tail of the pancreas should be resected because such lesions are associated with a high risk of metastatic disease.(Blansfield 2007) It is also recommended that tumors ≥2 cm in diameter that are located in the pancreatic head should also be evaluated for surgical resection, because selective removal of larger tumors carries risk of main pancreatic duct involvement and may require pancreaticoduodenectomy.(Keutgen 2016) Medical therapy for sporadic pNETs includes long-acting somatostatin agonists, targeted agents, and chemotherapeutic agents.(Caplin 2014, Raymond 2011) Prior approvals have typically included patients with progressive, unresectable, and locally-advanced or metastatic tumors and were based on randomized trials with a primary endpoint of progression-free survival. These therapies were characterized by low ORRs (5 to 13%).

Approved therapies for pancreatic neuroendocrine tumors

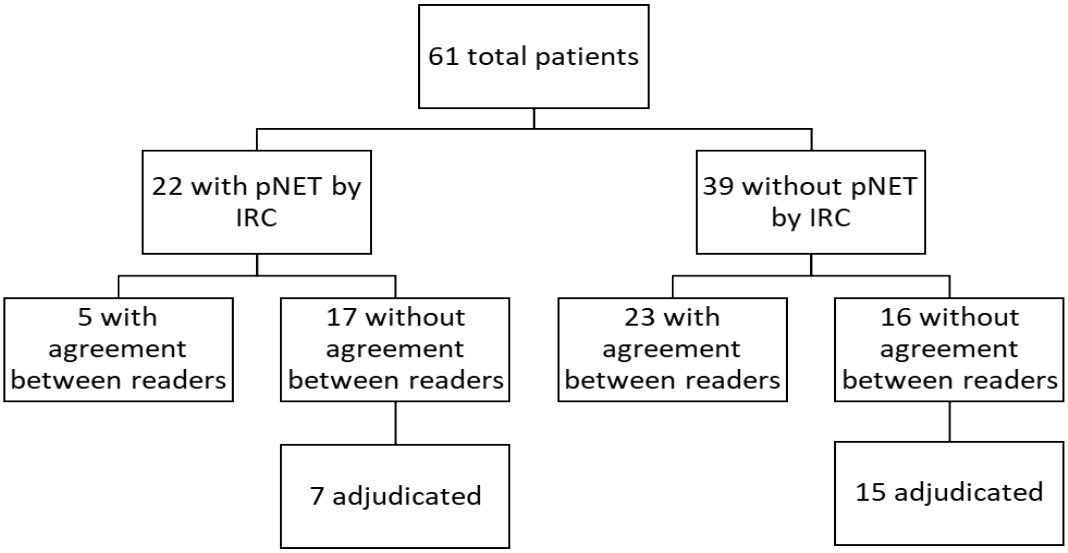
Drug	Eligibility	Design	N	Endpoint	Outcome
Sunitinib	Progressive, unresectable locally	Randomized, double-blind,	86, 85	PFS	mPFS: 10.2 vs.

	advanced/metastatic pNETs	placebo-controlled			5.4 mos. ORR: 9.3%
Everolimus	Nonfunctional, progressive, unresectable, locally advanced/metastatic pNETs	Randomized, double-blind, placebo-controlled	207, 203	PFS	mPFS: 11.4 vs. 5.4 mos. ORR: 4.8%
Lutathera	Progressive, unresectable locally advanced/metastatic GEP-NETs	Randomized, controlled *(high-dose octreotide control)*	116, 113	PFS	mPFS: NR vs. 8.5 mos. ORR: 12.9%
Lanreotide	Nonfunctional, unresectable locally advanced/metastatic GEP-NETs	Randomized, double-blind, placebo-controlled	101, 103	PFS	mPFS: NR vs. 16.6 mos. ORR: N/A

mPFS = median progression-free survival, ORR = overall response rate, GEP-NETs = gastroenteropancreatic-neuroendocrine tumors

Little data are available on the medical treatment of VHL-associated pNETs. Prospective single-arm study of pazopanib demonstrated partial responses in 9 of 17 patients (53%) with pancreatic lesions, however the majority of these lesions were serous cystadenomas and the number of pNETs that responded was not reported.(Jonasch 2018)

B) Data to support proposed labeling:
The Applicant submitted data on 22 patients determined to have pNETs per IRC review based on the data cut-off of Dec 2020. Review of the Applicant's response to information request dated June 6, 2021 revealed discordance between the two IRC readers that pNET existed at baseline in 17 of the 22 patients. Adjudication was performed in 7 of the 17 patients with disagreement. Review of the IRC pNET procedures document (Section 6.2) revealed that "adjudication will not occur for this pNET review". Adjudication was performed only for pancreatic lesions as a whole per the IRC pancreatic procedures document. These findings are summarized in the flowchart below.



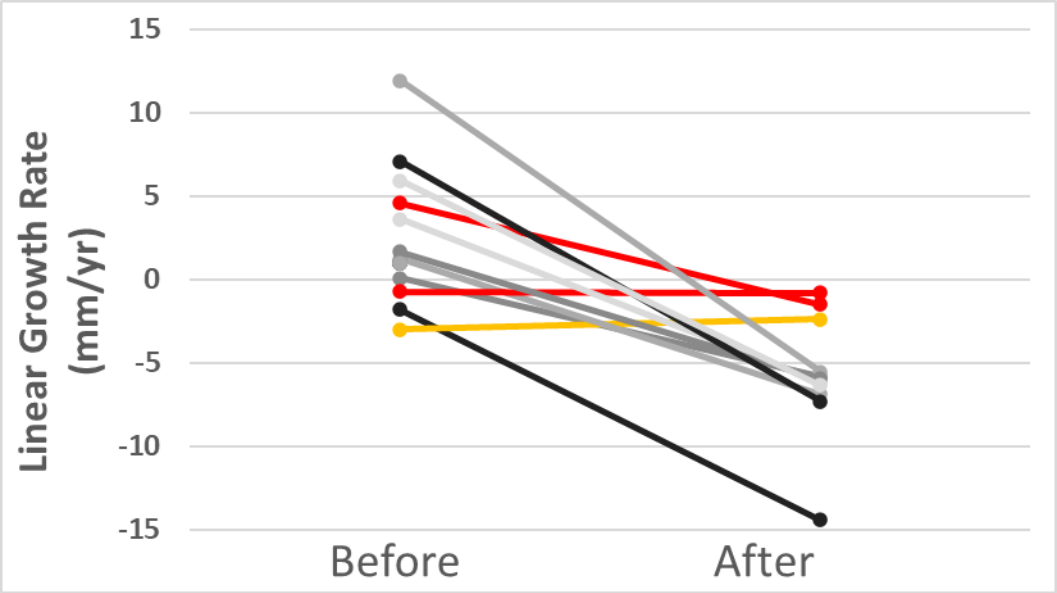
Therefore, a total of 12 patients had either agreement between primary IRC readers or positive adjudication that confirmed the presence of pNET at baseline. The Applicant provided the following rationale for this frequent discordance in their response to information request dated June 3, 2021:

1) *Frequent discordance between readers 1 and 2 is primarily due to a difference in the identification of pNET tumors*
2) *Scan acquisition was not optimized for pNET detection on a number of parameters, including contrast timing and slice thickness.*
3) *These scans were acquired to assess renal cell carcinoma, with pancreatic reviews added later to the study.*
4) *Intrinsic differences in pNET appearances on scans may also lead to discordance between primary readers.*
5) *All of these challenges are especially difficult in the setting of VHL disease where there may be a background of multiple pancreatic cystic lesions.*

Among the 12 patients with pNET at baseline per 2 radiologists, the ORR by IRC per RECIST v1.1 was 83.3% (95% CI: 51.6, 97.9). There were 2 CRs and 8 PRs. Five patients had a DOR > 12 months. The remaining 2 patients had stable disease. All patients had a reduction in sum diameters. There were no patients with progressive disease.

Linear growth rate data including at least 1 abdominal scan and IRC measurement prior to registration were available for 11 patients. Prior to treatment, 3 patients had regressing tumors, while 8 were progressive. All patients had negative growth after treatment. Two of the patients with previously regressing tumors had similar rates of regression after treatment and the third patient had a marked increase in the rate of regression after treatment. The mean growth rate prior to treatment was 2.8mm/year, whereas the mean growth

rate after treatment was -5.8mm/year (below, patients with best overall response of stable disease marked in red).



Information on tumor location (i.e. head, body, or tail of the pancreas) was not available, per the Applicant. No patient underwent surgery for pNET resection during the study period.

C) DO2 Recommendations:
DO2 recommends including VHL-associated pNETs in the indication statement or Section 14 of the beltuzifan label for the following reasons:

1) Indication statement: IRC analyses of VHL-associated pNETs in Study is 004 demonstrated objective responses in 10 of 12 patients. Imaging assessment was not optimized for pNET, but at least 2 radiologists agreed on the presence of pNET and observed responses in these 12 patients. There were no patients with progression. Despite the limited number of patients with confirmed pNET in this cohort, the number and depth of responses far exceeded those observed with currently approved therapies for sporadic pNET. In contrast to CNS hemangioblastomas, a small proportion of pNETs (20%) may demonstrate spontaneous regression. The ORR observed with belzutifan, including the lower bound of the 95% confidence interval (51.6%) exceeds this rate of spontaneous regression and linear growth rate data in patients with pNET supports a change in the growth kinetics after treatment. Given the observed responses with belzutifan in other tumor types and the shared pathogenic mechanisms in these tumors in VHL, the totality of evidence supports inclusion of pNETs in the indication statement. Given the median time to response of 8.1 months, this therapy is likely not appropriate for patients who require urgent intervention. We recommend the following indication statement:

Belzutifan is indicated for adult patients with VHL disease who require non-urgent treatment for pancreatic neuroendocrine tumors and who elect not to undergo surgery or for whom surgery is not considered appropriate.

2) Section 14: We recommend inclusion of ORR data in the table below:

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Median in months (range)	8.1 (2.7, 11.0)	3.1 (2.5, 11.0)

See Signature Page in DARRTS

V. References

1. Ammerman JM, Lonser RR, Dambrosia J, Butman JA, Oldfield EH: Long-term natural history of hemangioblastomas in patients with von Hippel–Lindau disease: implications for treatment. J Neurosurg 105:248–255, 2006
2. Arnon L: Impact of diagnosis with Pancreatic Neuroendocrine Tumors on Mortality in Patients with Von Hippel-Lindau Disease, in 14th International VHL Medical Research Symposium. 2020
3. Asthagiri AR, Mehta GU, Zach L, Li X, Butman JA, Camphausen KA, et al: Prospective evaluation of radiosurgery for hemangioblastomas in von Hippel-Lindau disease. Neuro Oncol 12:2010
4. Blansfield JA, Choyke L, Morita SY, Choyke PL, Pingpank JF, Alexander HR, et al: Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). Surgery 142:814-818.e2, 2007
5. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al: Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. N Engl J Med 371:224–233, 2014
6. Husstedt HW, Sickert M, Köstler H, Haubitz B, Becker H. Diagnostic value of the fast-FLAIR sequence in MR imaging of intracranial tumors. Eur Radiol. 2000;10(5):745-52. doi: 10.1007/s003300050997. PMID: 10823626.
7. Igarashi H, Ito T, Nishimori I, Tamura K, Yamasaki I, Tanaka M, et al: Pancreatic involvement in Japanese patients with von Hippel-Lindau disease: Results of a nationwide survey. J Gastroenterol 49:511–516, 2014
8. Jagannathan J, Lonser RR, Smith R, Devroom HL, Oldfield EH: Surgical management of cerebellar hemangioblastomas in patients with von Hippel–Lindau disease. J Neurosurg 108:210–222, 2008 Available: http://thejns.org/doi/abs/10.3171/JNS/2008/108/2/0210.
9. Jonasch E, McCutcheon IE, Gombos DS, Ahrar K, Perrier ND, Liu D, et al: Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. Lancet Oncol 19:1351–1359, 2018 Available: https://linkinghub.elsevier.com/retrieve/pii/S147020451830487X.
10. Kano H, Shuto T, Iwai Y, Sheehan J, Yamamoto M, McBride HL, et al: Stereotactic radiosurgery for intracranial hemangioblastomas: A retrospective international outcome study. J Neurosurg 122:1469–1478, 2015
11. Keutgen XM, Hammel P, Choyke PL, Libutti SK, Jonasch E, Kebebew E: Evaluation and management of pancreatic lesions in patients with von Hippel-Lindau disease. Nat Rev Clin Oncol 13:537–549, 2016
12. Krauss T, Ferrara AM, Links TP, Wellner U, Bancos I, Kvachenyuk A, et al: Preventive medicine of von Hippel-Lindau disease-associated pancreatic neuroendocrine tumors. Endocr Relat Cancer 25:783–793, 2018 Available: http://www.ncbi.nlm.nih.gov/pubmed/29748190.
13. Lonser RR, Butman JA, Huntoon K, Asthagiri AR, Wu T, Bakhtian KD, et al: Prospective natural history study of central nervous system hemangioblastomas in von Hippel-Lindau disease. J Neurosurg 120:1055–62, 2014

14. Mehta GU, Asthagiri AR, Bakhtian KD, Auh S, Oldfield EH, Lonser RR: Functional outcome after resection of spinal cord hemangioblastomas associated with von Hippel-Lindau disease. J Neurosurg Spine 12:233–242, 2010
15. Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al: Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 364:501–13, 2011 Available: http://www.ncbi.nlm.nih.gov/pubmed/21306237.
16. Taylor DG, Ilyas A, Mehta GU, Chen C-J, Schiff D, Oldfield EH, et al: Variable response of CNS hemangioblastomas to Pazopanib in a single patient with von Hippel-Lindau disease: Case report. J Clin Neurosci:2018
17. Tsuchiya K, Mizutani Y, Hachiya J. Preliminary evaluation of fluid-attenuated inversion-recovery MR in the diagnosis of intracranial tumors. AJNR Am J Neuroradiol. 1996 Jun-Jul;17(6):1081-6. PMID: 8791919
18. Weisbrod AB, Kitano M, Thomas F, Williams D, Gulati N, Gesuwan K, et al: Assessment of tumor growth in pancreatic neuroendocrine tumors in von Hippel Lindau syndrome. J Am Coll Surg 218:163–169, 2014 Available: http://dx.doi.org/10.1016/j.jamcollsurg.2013.10.025.
19. Wind JJ, Bakhtian KD, Sweet JA, Mehta GU, Thawani JP, Asthagiri AR, et al: Long-term outcome after resection of brainstem hemangioblastomas in von Hippel-Lindau disease. J Neurosurg 114:2011

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/s/

GAUTAM U MEHTA
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 23, 2021
To:	Jeannette Dinin Regulatory Project Manager **Division of Oncology 1 (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Dvorsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	WELIREG (belzutifan)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215383
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On January 15, 2021, Merck Sharp & Dohme Corp. submitted for the Agency's review the final part of their Rolling Submission of an Original New Drug Application (NDA) 215383 for WELIREG (belzutifan) tablets. The proposed indication for WELIREG (belzutifan) is for the treatment of patients with Von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery. We note that the proposed proprietary name WELIREG was found to be conditionally acceptable on March 15, 2021 by the Division of Medication Error, Prevention, and Analysis (DMEPA).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 1 (DO1) on January 25, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for WELIREG (belzutifan) tablets. On May 18, 2021, DO1 requested the Applicant to revise the PPI to a Medication Guide (MG).

2 MATERIAL REVIEWED

- Draft WELIREG (belzutifan) MG received on May 27, 2021, and received by DMPP and OPDP on July 16, 2021.
- Draft WELIREG (belzutifan) Prescribing Information (PI) received on January 15, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 16, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the font size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 22, 2021

To: Jeannette Dinin, BS, Regulatory Project Manager
Division of Oncology 1 (DO1)

From: Emily Dvorsky, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for WELIREG™ (belzutifan) tablets, for oral use

NDA: 215383

In response to DO1 consult request dated January 25, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for WELIREG™ (belzutifan) tablets, for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO1 (Jeannette Dinin) on July 16, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 30, 2021 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or Emily.Dvorsky@fda.hhs.gov.

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EMILY M DVORSKY
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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research, CDER
Office of Immunology and Inflammation, OII
Division of Gastroenterology, DG

Date:	April 30, 2021
From:	Aysegul Gozu MD, MPH, Clinical Reviewer, Division of Gastroenterology (DG)
Through:	Erica Lyons MD, Associate Director for Therapeutic Review, DG Juli Tomaino, MD Deputy Director, DG
Submission Number:	NDA 215383
Requested By:	Jeannette Dinin Division of Regulatory Operations Office of Regulatory Operations for Oncologic Diseases
Sponsor:	Merck Sharp and Dohme Corp.
Product:	Belzutifan (Welireg)
Date of Request:	December 29, 2020
Proposed Indication:	Renal Cell Carcinoma (RCC) associated with von Hippel-Lindau (VHL) disease
Reason for Consultation:	VHL disease-associated pancreatic tumors

Introduction

The Division of Regulatory Operations, Office of Regulatory Operations for Oncologic Diseases, Division of Oncology 1 (DO1) has requested a consultation from Office of Immunology and Inflammation (OII), Division of Gastroenterology (DG), *"to assess the safety and efficacy of this drug in comparison with currently available treatment options for von Hippel-Lindau (VHL)-disease associated pancreatic lesions,* (b) (4)

Belzutifan (MK-6482) is a small molecule and first-in-class inhibitor of hypoxia-inducible factor (HIF)-2 alpha which impairs hypoxic and pseudohypoxia signaling in cancer cells. In tumor cells where HIF-2 alpha is activated, belzutifan blocks the transcription of several genes involved in oncogenesis. According to the Applicant, bezultifan has shown antitumor activity in mouse xenograft models of clear cell renal cell carcinoma (ccRCC), resulting in tumor stasis or regression after oral administration.

Belzutifan is being developed for the treatment of patients with VHL disease associated RCC, not requiring immediate surgery. There are no currently approved drugs for the proposed indication or other VHL-associated tumors.

Von Hippel-Lindau (VHL) Pancreas Lesions- Cysts, Cystadenomas, and Tumors

Pancreatic cysts, cystadenomas, and tumors occur in 17 to 77% of patients with VHL disease (Charlesworth et al., 2012; Hammel et al., 2000; Kobayashi et al., 2012). Most patients with pancreatic lesions have no symptoms, and the lesions are usually identified during VHL screening. Approximately 80-90% of identified pancreatic lesions are single or multiple pancreatic cysts and 10 to 17% are pNET or cystadenomas (Blansfield et al., 2007). Malignant transformation of pNET may occur in up to 17% of these patients. Pancreatic adenocarcinomas and metastases from RCC are very rare, with metastatic disease reported in only 0.4% to 3% of surgically resected pancreatic tumors (Charlesworth et al., 2012; Hammel et al., 2000).

The progression of pancreatic cysts and cystadenomas are not predictable and vary between patients with lesions increasing, decreasing, or remaining stable in size over time. Hammel et. al reported that in approximately half of the patients with pancreatic cysts (single or multiple), the cyst size changed during 30-month follow up. Of these, 66% increased in size and 33% decreased in size. Lesions were noted to increase in size in only 30% of patients with cystadenomas.

Although majority of pancreatic lesions (cysts and cystadenomas) are benign and asymptomatic, these lesions may rarely cause symptoms due to enlarged size and local compression of the intestine, pancreas, or bile duct. As stated above, surgical intervention for benign tumors is reserved for those with symptomatic disease.

Study MK-6482-004

Study MK-6482-004 was a single-arm, open-label phase 2 study to evaluate the efficacy and safety of belzutifan for the treatment of VHL disease-associated RCC as measured by overall response rate (ORR) per RECIST 1.1[1]. The study enrolled 61 patients with VHL disease who had at least one measurable solid tumor localized to the kidney and who did not require immediate surgery. Patients received belzutifan 120 mg once daily until progression of disease or unacceptable toxicity. Patients were evaluated radiologically approximately 12 weeks before the initiation of treatment and every 12 weeks thereafter while continuing in the study to assess response to treatment for VHL disease associated RCC and non-RCC areas of disease that were present at screening per investigator.

Patients in the study population had a median age of 41 years, 52.5% were male, and 90.2% were white. Seventy-seven percent (77%) of patients had prior surgical procedures for RCC. Fifty patients (82%) had CNS hemangioblastomas, 61 patients (100%) had pancreatic lesions (pNET and non-pNET), and 20 patients (33%) had pNETs based on the report of the central independent review committee (IRC).

[1] RECIST (Response Evaluation Criteria in Solid Tumors) is a set of published rules that define when cancer patients improve ("respond"), stay the same ("stable"), or worsen ("progression") during treatment. RECIST 1.1, published in January 2009, is an update to the original criteria published in February 2000.

Assessment of Pancreatic Lesions

Pancreatic lesions were selected by the IRC as targets (i.e., measured lesions during the study) or non-targets out of all the available VHL-associated lesions (e.g., pNET and also non-pNET) and the sum of diameters was then assessed in order to determine response. The efficacy endpoints included: overall response rate (ORR), disease control rate (DCR), and duration of response (DOR). Information regarding locations of the lesions in the pancreas was not captured in Applicant's database.

The study reported a discrepancy in the number of patients with pancreatic lesions at baseline per the IRC review (n=61) and per the investigator assessment (n=31). The Applicant initially stated that the discrepancy could be explained by IRC accounting for both cystadenomas and pNETs while some investigators chose only to assess pNETs as target lesions.

On March 16, 2021, FDA requested clarification of the clinical data, specifically pertaining to pancreatic lesions. A response was requested by March 22, 2021. Subsequently, FDA extended the response deadline to March 26, 2021, per the Applicant's request.

The Applicant provided further explanation for the discrepancy in reporting in the response to the IR and confirmed that, in study MK-6482-004, all 61 patients presented with baseline pancreatic lesions, including pNET and/or non-pNET lesions according to the Pancreatic Independent Review Procedures Documents. The Applicant stated that MK-6482-004 was designed to primarily focus on VHL-disease associated RCC, and assessment of response in pancreatic lesions was defined as a secondary objective.

The Applicant further commented that there were no protocol-defined selection criteria for pancreatic lesions despite the heterogeneous pathology associated with pancreatic lesions in patients with VHL. As a result, the investigators had taken different approaches in selecting pancreatic lesions at baseline. Of the 31 patients reported to have pancreatic lesions at baseline assessed by the investigators, 11 patients had "pNET only", 14 patients had "cystic lesions/cystadenomas only", and 6 patients had "pancreatic lesions". The IRC evaluation of pancreatic lesions included pNET and non-pNET lesions at baseline based on the pNET Independent Review Procedures Documents. Thus, the discrepancy between the numbers of pancreatic lesions at baseline as assessed by investigators (n=31) vs. IRC (n=61) was attributed to the difference in lesion selection criteria by the investigator vs. by the IRC in addition to a lack of protocol-defined specific selection criteria in the context of highly heterogeneous nature of the pancreatic lesions manifested in VHL disease. Although the Applicant initially stated in the IR response that pancreatic single cysts and multiple cysts were not evaluated in Study MK-6482-004, they later defined non-pNET lesions as both cystic lesions and cystadenomas.

The Applicant stated that non-PNET lesions included a wider scope of cystic lesions (cystic lesions /cystadenomas) rather than strictly cystadenomas due to the following reasons:

1. Non-pNET lesions were not further sub-classified as it was not required per the pNET Independent Review Procedural Document, and

2. Aforementioned extreme complex morphological manifestations associated with the pancreatic lesions pose significant challenges in distinction of cystic lesions /cystadenomas unless specific criteria are clearly defined.

Also, in response to the IR, the Applicant provided the types of pancreatic lesions (pNET and non-pNET) at baseline according to the IRC. Twenty (20) patients had pNETs; 44 patients had non-pNET lesions; 3 patients had both pNETs and non-pNET lesions at baseline. The Applicant also stated that since non-pNET lesions included both cystic lesions and cystadenomas in the IRC review, the rate of non-pNET was higher than the reported rate for cystadenomas alone in the available supportive literature.

Among the 61 patients with identified pancreatic lesions, the ORR was 64% (39/61); 4 patients achieved complete response and 35 patients achieved partial response. The median DOR was not reached and based on Kaplan-Meier estimation, 94% of responders had an ongoing response at 12 months. The median TTR was 35 weeks, median PFS and TTS were not reached. As study MK-6482 consisted of a single-arm, open-label evaluation, no comparative data were available for the rate of spontaneous regression or resolution of these lesions. As previously described, the progression of pancreatic cysts and cystadenomas are not predictable and vary between patients with lesions increasing, decreasing, or remaining stable in size over time; therefore, it is difficult to determine whether the single-arm, open-label data represent a meaningful change in these lesions.

(b) (4)

Safety Evaluation

The most common AEs (≥20% incidence) were anemia (90.2%), fatigue (60.7%), headache (37.7%), dizziness (36.1%), and nausea (31.1%). The most frequent Grade 3 to 5 AEs (more than1 patient) were anemia (6.6%), fatigue (4.9%), and hypertension (3.3%). No treatment-related Grade 4 or Grade 5 events occurred. Drug-related AEs leading to dose interruption occurred in 14 patients (23.0%), dose reduction in 6 patients (9.8%) and dose discontinuation in 1 patient (1.6%).

Important ADRs for belzutifan included anemia due to decreased erythropoietin and hypoxia. Grade 3 anemia occurred in 4 patients (6.6%). Grade 3 hypoxia occurred in 1 patient (1.6%). Overall, most cases of anemia were mild to moderate, and managed with the administration of an erythropoietin stimulating agent and/or blood transfusion along with dose interruption or reduction.

Conclusions on the Demonstration of Benefit

Study MK-6482-004 was designed to characterize the effect of treatment with belzutifan on RCC in patients with VHL disease. Although assessment of response for pancreatic lesions was defined as a secondary objective, there were no protocol-defined selection criteria for these lesions despite the heterogeneous presentation known to occur in patients with VHL. Accordingly, there was a noteworthy discrepancy between lesions identified by the IRC and those identified by investigators. Without standard classification and agreement on lesion identification, the ability of the data to support the evaluation of a treatment effect is significantly limited.

(b) (4)

Although the natural history of these lesions has not been well-characterized, in patients with non-pNET pancreatic lesions have been shown to have a heterogenous rate of progression that includes spontaneous regression and resolution. Furthermore, there is no known association between tumor size for these lesions and clinical outcomes. Although benign pancreatic lesions are very common in von Hippel-Lindau disease, these vast majority of these lesions do not cause symptoms or require medical or surgical intervention (Charlesworth et al., 2012; Mukhopadhyay et al., 2002).

In the absence of data to support a treatment effect above that expected based on the natural history of these lesions, evidence is lacking to support that a decrease or maintenance of stability in size for these lesions is predictive of a clinical benefit for patients.

(b) (4)

References

Blansfield, J. A., Choyke, L., Morita, S. Y., Choyke, P. L., Pingpank, J. F., Alexander, H. R., . . . Libutti, S. K. (2007). Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). *Surgery, 142*(6), 814-818; discussion 818.e811-812. doi:10.1016/j.surg.2007.09.012

Charlesworth, M., Verbeke, C. S., Falk, G. A., Walsh, M., Smith, A. M., & Morris-Stiff, G. (2012). Pancreatic lesions in von Hippel-Lindau disease? A systematic review and meta-synthesis of the literature. *J Gastrointest Surg, 16*(7), 1422-1428. doi:10.1007/s11605-012-1847-0

Hammel, P. R., Vilgrain, V., Terris, B., Penfornis, A., Sauvanet, A., Correas, J. M., . . . Richard, S. (2000). Pancreatic involvement in von Hippel-Lindau disease. The Groupe Francophone d'Etude de la Maladie de von Hippel-Lindau. *Gastroenterology, 119*(4), 1087-1095. doi:10.1053/gast.2000.18143

Kobayashi, N., Sato, T., Kato, S., Watanabe, S., Hosono, K., Shimamura, T., . . . Kubota, K. (2012). Imaging findings of pancreatic cystic lesions in von Hippel-Lindau disease. *Intern Med, 51*(11), 1301-1307. doi:10.2169/internalmedicine.51.7194

Mukhopadhyay, B., Sahdev, A., Monson, J. P., Besser, G. M., Reznek, R. H., & Chew, S. L. (2002). Pancreatic lesions in von Hippel-Lindau disease. *Clin Endocrinol (Oxf), 57*(5), 603-608. doi:10.1046/j.1365-2265.2002.01637.x

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Medical Officer's Review of NDA 215383
Ophthalmology Consultant Review #2

NDA 215383

Submission: 3/19/2021
Review completed: 4/19/2021

Name: Belzutifan

Applicant: Merck Sharp & Dohme Corp

Pharmacologic Category: Inhibitor of HIF-2α,

Indications: Treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery.

Submitted: Response by Merck to FDA's March 5, 2021, requested safety information related to the submitted ophthalmology data under NDA 215383.

ORIGINAL AGENCY COMMENT:
Question 1. Patient (b) (6) is reported as having a retinal detachment. The eye with the retinal detachment has not been identified. The investigator classified the event as not related to treatment and related to pre-existing lesions related to Von Hippel-Lindau disease; however, one of the eyes did not have any evidence of retinal disease. Even for eyes with retinal lesions, all retinal lesions do not lead to retinal detachments. Retinal detachments were not listed in the Investigator Brochure as a potential consequence of retinal lesions. Both eyes of this subject lost visual acuity. The eye with the retinal detachment should be identified; additionally, provide an explanation as to why this retinal detachment should not be classified as drug related.

COMPANY RESPONSE:
Participant (b) (6) is a 65-year old white female patient with VHL disease involving retinal (since 1989), renal, CNS and pancreatic manifestations. She developed Grade 4 retinal detachment in the right eye 8 days after having received the first dose of belzutifan treatment. Relevant medical history includes laser/cryotherapy for retinal hemangiomas in right eye (date not provided) and high myopia in both eyes.

The participant started treatment with belzutifan (120 mg, QD) on (b) (6). On (b) (6), she sought treatment for blurring of vision and multiple floaters in the right eye and was diagnosed with retinal detachment. Belzutifan was interrupted; the participant subsequently received vitrectomy (retinal detachment repair) on (b) (6). On (b) (6), the event was considered revolved, and belzutifan was resumed at the same dose, which was 28 days after the onset of the event.

From (b) (6) to (b) (6), the participant experienced additional vision-related AEs, including 1) 3 episodes of Grade 1 floaters on (b) (6) (left eye) and (b) (6) (left eye), both

resolved on the same day; 2) Grade 1 blurry vision (both eyes), onset (b) (6) (onset) to (b) (6) (resolved). All events were assessed by the investigator as unlikely or not related to belzutifan, and no actions were taken on belzutifan dosing and no treatments were given for these events.

On (b) (6), the participant had her most recent scheduled study visit (week 97). She continues to receive belzutifan to date, and no recurrence of retinal detachment has been reported.

According to the investigator and the consulting ophthalmologists, "the participant in question experienced a rhegmatogenous retinal detachment in the right eye secondary to a macular hole approximately a week following start of study medication. In our judgment, the retinal detachment was the result of an uncommon constellation of factors active before study enrollment, including presence of large retinal hemangioblastomas (including a posterior lesion causing massive exudation in the macula), presence of epiretinal membranes exerting traction on the macula, and co-existent high myopia, which is known to cause rhegmatogenous retinal detachments from macular hole formation. The severe ocular VHL disease in this eye was refractory to treatment with intravitreal bevacizumab injections prior to study entry. The retinal detachment was treated appropriately with surgical repair (vitrectomy), and there has been no recurrence of retinal detachment during the study.

Retinal exudation has improved in the right eye during the study, attributable to beneficial effect of the study drug. The left eye was noted to have high myopia and presence of punctate retinal hemangioblastomas at baseline but has maintained good vision during the study to date. The floaters reported during the study are consistent with symptoms attributable primarily to the myopia. Please also note that the visual acuity prior to the initiation of the drug remained the same in the left eye (20/25) while the right eye had a decrease during the retinal detachment and the surgical repair. At the last study visit, the visual acuity in the right eye is similar to pre-treatment level (20/80)."

Reviewer's Comments: *This rhegmatogenous retinal detachment secondary to a macular hole in a high myope is unlikely to be related to the drug product or the disease condition.*

Applicant's conclusion:
A comprehensive review of available literature, preclinical, and clinical safety data does not suggest an increased risk of retinal detachment associated with belzutifan. The underlying etiologies for the single case of Grade 4 retinal attachment in participant (b) (6) were primarily attributed to the pre-existing retinal hemangioblastomas, pre-existing macula abnormality and high myopia as described above. Previous treatment with laser/cryotherapy and intraocular bevacizumab were additional confounding factors for retinal detachment from the known lesion. Furthermore, considering the nature and severity of the event in relation to the relative short time-to-onset, and the negative re-challenge, the Sponsor agrees with the Investigator's assessment that Grade 4 retinal attachment was not related to belzutifan.

Reviewer's Comments: *The applicant's conclusion above does not appear to recognize the difference between retinal detachments due to macular holes in high myopes and events related to retinal hemangioblastomas and their treatment.*

ORIGINAL AGENCY COMMENT:
Question 2. Patient [redacted] is reported as having a retinal vein occlusion. Retinal vein occlusions are potentially sight threatening. Provide an explanation as to why this event is listed as a Grade 2 event and why it is not listed as drug related.

COMPANY RESPONSE:
Participant [redacted] is a 53-year old white female patient with VHL disease involving retinal, renal, and CNS manifestations; she developed Grade 2 central retinal vein occlusion (CRVO) in the right eye approximately 16 months after having received the first dose of belzutifan treatment.

Severity of the event of CRVO was assessed and reported by the investigator as Grade 2 based on CTCAE v.4.03 for thromboembolic event, see below (yellow highlighted): This was the most appropriate CTCAE term and category identified by the investigator for this event.

The participant had received laser treatment for retinal hemangiomas in the left eye ([redacted] and [redacted]), left partial nephrectomies and right kidney cryotherapy. Additional relevant medical history include hypertension ([redacted], with ramipril treatment since [redacted]), no prior history of deep vein thrombosis (DVT), non-smoker; no other concomitant medications received prior to the onset of the CRVO.

The participant started treatment with belzutifan (120 mg, QD) on [redacted]. On [redacted], the participant developed almost complete loss of vision in the right eye(vision acuity not reported) following 2 weeks of blurred vision; vision in the left eye was normal. She was diagnosed with central retinal vein occlusion (CRVO) as a result of venous thrombosis with almost total occlusion (90%) in the right eye. On [redacted], relevant lab findings showed elevated total cholesterol (7.1 mmol/L, upper limit normal 5 mmol/L) and elevated LDL (5.0 mmol/L, upper limit normal 3.0 mmol/L). Atorvastatin (20 mg, QD) was started on [redacted] for elevated cholesterol and the participant remains on atorvastatin to date. Ezetimib (10 mg, QD) was added since [redacted] for elevated cholesterol.

The investigator confirmed no prior history of thrombosis; diagnostic tests on anticoagulative disorders were without positive findings, and platelet counts were normal. ECGs have been normal since baseline. On [redacted], MRI of the brain showed diffuse edema periorbital on right side, but normal findings retrobulbus and in relation to sinus; no tumors in orbita.

Belzutifan was held from [redacted] to [redacted] and was resumed on [redacted] at the same dose. On [redacted], the participant experienced G3 hypertension (hypertension worsening, 145/95 mmHg); ramipril dose was increased to 7.5 mg, QD (previously 2.5 mg QD since [redacted]). The event resolved on [redacted], and ramipril was discontinued. Since [redacted], the patient received intravitreal injection of angiostatic drug (aflibercept), with the last dose on [redacted]. There has been no improvement of vision in the right eye. Grade 2 central retinal vein occlusion remains unresolved; the condition is considered permanent according to the investigator. On [redacted], the participant had her most recent scheduled study visit (week 109) and continues to receive belzutifan to date.

The investigator assessed that CRVO was related to hypertension and elevated cholesterol which

are significant confounding factors for venous thrombosis and was not related to belzutifan.

Preclinical evaluation regarding coagulation:
In addition, there were no changes in coagulation parameters (PT and APTT) and platelet counts in nonclinical studies with belzutifan. In the GLP toxicology studies of 4-week and 3- month duration in rats and dogs, an assessment of coagulation parameters and hematology was performed on all dogs once during the pre-dose period and on all dogs once towards the end of the dosing period, and all rats once towards the end of dosing period. The coagulation evaluation and platelet count did not identify any belzutifan-related effects in rats administered up to 200 mg/kg/day or dogs administered up to 30 mg/kg/day belzutifan.

Further, as described in the response to the Question 1, there were no belzutifan-related changes in eyes of these animals in the gross and histo-morphologic examinations.

Analysis of Similar Events on the Safety and Clinical Database
The Company's global safety database and clinical database was queried to identify similar cases from studies MK-6482-001 and MK-6482-004 through 01-Jun-2020. The search strategy included the narrow SMQ for Retinal disorders and the narrow SMQ for Embolic and thrombotic events, venous (MedDRA version 23.1). In the global safety database, one case of retinal detachment in participant 032-027 was identified. This case is described above in Question 1. In the clinical database, two further cases were identified. One case of Grade 1 vitreous floaters, assessed as unrelated to MK-6482, was identified in MK-6482-001, and one case of Grade 2 deep vein thrombosis (DVT), assessed as unrelated to MK-6482 was identified in MK-6482-001. The patient with vitreous floaters had relevant medical history of hypertension (1989), hyperlipidemia (1992), stroke (1992), TIA (2011), and peripheral vascular disease (2014). The patient with DVT had a history of renal hypertension, deep vein thrombosis in leg(s) since 2013, neuropathy peripheral since 2015, and edema of lower extremities since 2017. Both participants continued study without treatment modification.

Conclusion:
A review of literature, preclinical and clinical safety data does not indicate any significant evidence to suggest belzutifan is associated with coagulation abnormality, platelet count increase or increased risk of thromboembolism. Pre-existing hypertension and hypercholesterolemia are significant risk factors for CRVO reported in this patient; the Sponsor agrees with the investigator's assessment that CRVO was not related to belzutifan.

Reviewer's Comments: *The classification of an event with "almost complete loss of vision" as a Grade 2 event is not correct. The event should be classified as Category 4 when the visual acuity is less than 20/200.*

ORIGINAL AGENCY COMMENT:
Question 3. Study MK-6482-004 is reported as having 28% of patients with retinal hemangioblastomas at screening. The IRC assessment of retinal hemangioblastomas was limited to those participants for whom investigators had originally assessed as having retinal hemangioblastomas at screening. The Von Hippel-Lindau Natural History Study, Epidemiology No. EP05047.001, VEAP #: 9038 reports retinal hemangioblastomas in twice

as many patients (57%). An included reference article, Survey of Ophthalmology, Volume 46(2), Sept-Oct 2001, reports a frequency of retinal hemangioblastomas of 50-60%. Provide an explanation on whether there is a likely reason why the population studied in MK-6482-004 does not appear to be representative of the typical Von Hippel-Lindau population.

COMPANY RESPONSE:
The estimated percentage of patients with retinal hemangioblastoma (RH) from MK-6482-004, the VHL Natural History Study (EP05047.001), and the published literature represent different types of prevalence estimates, and caution should be exercised when comparing across studies and populations.

In MK-6482-004, the RH prevalence estimate describes the percentage of renal cell carcinoma (RCC) patients with concurrent RH lesions at screening. Conversely, in the VHL Natural History Study, the RH prevalence estimate is a lifetime prevalence estimate at the patient level index date, or cohort entry date, and describes the proportion of RCC patients with a history of RH tumors detected at some point during routine clinical care prior to the patient level index date. It is possible that patients may have received prior RH treatment by the time they entered the natural history study cohort. The percentage of patients in the VHL Natural History Study with concurrent RH tumors at the patient-level index date is not currently available. Even when describing concurrent disease, there is likely significant variability of estimates based on different data sources, study designs, populations, small patient counts, etc. A few published estimates from other VHL RCC studies show the frequency of concurrent RH disease has ranged from approximately 15-50% (Peng 2019; Zhang 2012; Roma 2015).

It is also important to recognize that other prevalence estimates in the published literature are estimates for a broad VHL patient population, including those with and without RCC manifestations. Some estimates represent lifetime prevalence estimates for patients with VHL disease (Singh A, 2015), with a few additional publications of small Phase 2 clinical investigations with estimates of concurrent RH disease estimates ranging from 9-60% (Jonasch 2011; Jonasch 2018). Differences in estimates across the published literature may reflect variation in populations, study designs, and sampling variability given small patient counts. That being said, based on the available data, there is no reason to suspect the population studied in MK-6482-004 is not representative of patients with VHL disease-associated RCC as it relates to the frequency of concurrent disease.

Reviewer's Comments: *Disagree. Based on the natural history study and the literature, the prevalence of ocular findings was lower than expected in the submitted study. This raises concern that the population included was on the milder end of the disease spectrum.*

ORIGINAL AGENCY COMMENT:
Question 4. Retinal angiomas were assessed by an independent central committee of ophthalmologists, reviewing fundoscopic images. A copy of the fundoscopic images that were assessed and a copy of all reports by the independent central committee of ophthalmologists should be submitted to the NDA.

COMPANY RESPONSE:
The fundoscopic imaging data from evaluable patients are now submitted to NDA under Module 5.3.5.2. The assessment of retinal angiomas is described in the excel spreadsheet associated with the images (under Module 5.3.5.2). Images are labelled with patient's ID and visit number, which match the assessment in the excel spreadsheet.

Reviewer's Comments: *The fundoscopic imaging data was reviewed. The images are generally of low quality, and it is not possible to accurately determine improvement from these images.*

Summary:

1. As noted in the first ophthalmology consult review, only 5 eyes (4 subjects) demonstrated improvement in retinal lesions without potentially confounding circumstances. This assessment was made based on the ophthalmologist's examination. The majority of eyes reported as stable or improved in the trial did not have any lesions at baseline. It is not possible to accurately determine improvement from the images that have been submitted.

2. Patient (b) (6) is reported as having a retinal vein occlusion and having "an almost complete loss vision." The event was incorrectly classified as a Grade 2 event. The event (if classified) should be classified as a Grade 4 event.

3. Study MK-6482-004 is reported as having 28% of patients with retinal hemangioblastomas at screening. Based on the natural history study and the literature, the prevalence of ocular findings was lower than expected in the submitted study. This raises concern that the population included was on the milder end of the disease spectrum.

4. The fundoscopic imaging data was reviewed. The images are generally of low quality, and it is not possible to accurately determine improvement from these images.

Wiley A. Chambers, M.D.
Supervisory Physician, Ophthalmology

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 14, 2021
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 215383
Product Name, Dosage Form, and Strength:	Welireg (Belzutifan) tablets, 40 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
FDA Received Date:	January 15, 2021
OSE RCM #:	2021-52
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the review process for Welireg (Belzutifan) tablets, the Division of Oncology 1 (DO1) requested that we review the proposed Welireg prescribing information, Patient Information, and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Welireg PI and determined that it may be improved to clarify important information.

We reviewed the proposed Welireg container label and proposed Patient Information and find them acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Welireg container label and Patient Information are acceptable from a medication error perspective. The proposed Welireg PI may be improved for clarity. We provide specific recommendations in Section 4.1 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. Dosage and Administration Section

a. Consider relocating the statement [redacted] (b) (4) after the dosage statement for clarity.

b. Consider [redacted] (b) (4) for clarity. For example, "Advise patients to swallow tablets whole. Do not chew, crush, or split WELIREG prior to swallowing. WELIREG may be taken with or without food."

c. As currently presented, the statement "Resume at a reduced dose [redacted] (b) (4)" is unclear whether the reduced dose should be 80 mg or 40 mg. We recommend clarifying this statement with the exact dose [redacted] (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Welireg received on January 15, 2021 from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Table 2. Relevant Product Information for Welireg	
Initial Approval Date	N/A
Active Ingredient	Belzutifan
Indication	treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery.
Route of Administration	oral
Dosage Form	tablets
Strength	40 mg
Dose and Frequency	120 mg (three 40 mg tablets) once daily
How Supplied	Bottle of 90 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F)
Container Closure	100 cc high density polyethylene (HDPE) bottle with induction seal closure and desiccant

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Welireg labels and labeling submitted by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

- Container label received on January 15, 2021
- Prescribing Information (Image not shown) received on January 15, 2021, available from \\CDSESUB1\evsprod\nda215383\0006\m1\us\01-crt-uspi-mk6482-t-original.doc
- Patient Information received on January 15, 2021, available from \\CDSESUB1\evsprod\nda215383\0006\m1\us\01-crt-usppi-mk6482-t-original.doc

G.2 Label and Labeling Images

Container label

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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ASHLEIGH V LOWERY
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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 215383
Submission Number	002 and 006
Submission Date	12/15/2020
Date Consult Received	2/17/2021
Drug Name	Welireg (belzutifan)
Indication	Von Hippel-Lindau disease-associated renal cell carcinoma.
Therapeutic dose	120 mg, once daily
Clinical Division	DO1

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 2/17/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND-132120 dated 02/14/2019 in DARRTS (link);
- Sponsor's clinical study protocol # PT2977-202 (SN0001; link);
- Sponsor's clinical study report # P004V01MK6482 (SN0001; link);
- Sponsor's statistical analysis plan # P004V01MK6482 (SN0002; link);
- Sponsor's cardiac safety report # P004V01MK6482 (SN0002; link);
- Sponsor's proposed product label (SN0006; link);
- Investigator's brochure Ver 7.0 (SN0002; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0002; link).

1 SUMMARY

No large QTc prolongation effect (i.e., >20 msec) of belzutifan was observed in this QT assessment of belzutifan. We are reluctant to draw conclusions of lack of an effect in the absence of a positive control, large exposure margin, or an integrated nonclinical safety assessment conduct according to best practices (ICH S7b Q&A 1.1 and 1.2).

The effect of belzutifan was evaluated in study 3 PT2977-202 (MK6482-004). This was an open-label Phase 2 study evaluating the efficacy and safety of PT2977 in patients with von Hippel-Lindau disease. The highest dose evaluated was 120 mg once daily which covers the therapeutic exposures. The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that belzutifan is associated with large mean increases in the QTc interval (refer to Section 4.5) – see Table 1 for overall results.

The findings of this analysis are further supported by the available nonclinical data (Sections 3.1.2) and by time analysis (Section 4.3) and categorical analysis (Section 4.4).

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF (FDA Analysis)

ECG Parameter	Treatment	Concentration (ng/mL)	ΔQTcF (msec)	90% CI (msec)
QTc	Belzutifan 120 mg*	1380	2.5	(0.6 to 4.4)

**Subjects revived 120 mg once daily (week 3); For further details on the FDA analysis, please see Section 4.*

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SN006 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At the recommended dose, (b) (4) TRADEMARK (b) (4) does not cause large mean increases (i.e., > 20 msec) in (b) (4) the QT interval (b) (4)

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Merck & Co., Inc., is developing belzutifan for the treatment of patients with von Hippel-Lindau disease-associated renal cell carcinoma (not requiring immediate surgery). Belzutifan (MK-6482, PT2977, CK 1604; MW: 383.34 g/mol) is inhibitor of hypoxia-inducible factor 2α (HIF-2α). The sponsor states that belzutifan exhibits its antineoplastic activity by preventing HIF-2α heterodimerization and its subsequent binding to DNA.

The product is formulated as immediate-release film-coated tablet formulation containing 40 mg belzutifan for oral administration. The maximum proposed therapeutic dose for the present indication is 120 mg once daily which is being evaluated in the ongoing Phase-3 study. The peak concentrations of ~1360 ng/mL (Tmax: ~1.5 h; half-life: ~15 h) are expected at steady-state with the anticipated therapeutic dose in advanced RCC patients (POP-PK Predicted). No significant accumulation is expected at steady-state with the proposed maximum therapeutic dose (120 mg once daily; Cmax Racc: ~1.33; POP-PK). However, higher exposures were observed (Cmax: 1787; Day 15) in cancer patients with advanced solid tumors and advanced RCC (Study # MK-6482-001; fasting). The maximum tolerated dose is not established, and the maximum studied dose is 240 mg once daily (Cmax,ss: 2480 ng/mL; RCC patients).

The studies indicate that belzutifan is mainly metabolized by the polymorphic enzymes UGT2B17 (forming major metabolite; glucuronide PT3317) and CYP2C19. Based on the POP-PK analysis, the subjects with poor metabolizer (dual PM) of UGT2B17 and CYP2C19, are expected to have increased exposures of belzutifan (2.3x) compared to those with normal metabolizers. No formal clinical drug interaction studies have been conducted by the sponsor (as victim drug). Belzutifan exhibits a slight negative food effect with a small decrease in peak concentrations (GMR; Cmax: ~0.65 and AUC: ~0.97) was observed following its administration with a high-fat and high-calorie meal compared to that under fasting condition (Study # P002 MK6482). The product is intended to be administered with or without food.

Previously, the IRT reviewed the sponsor's request for substitution of thorough QT study. The sponsor proposed to use PK/ECG data from their clinical studies (Study # PT2977-101 and Study # PT2977-202). Refer to the previous IRT review under IND-132120 dated 02/14/2019 in DARRTS (link). Although, the study # PT2977-202 appeared reasonable to exclude large mean increases (i.e., > 20 msec), it was unclear if the exposures of PT2977 achieved in this study would be adequate to conduct meaningful concentration-QTc analysis.

Recently, the sponsor submitted their cardiac safety assessment report (Study # PT2977-202 or MK-6482-004). This was an open-label Phase 2 study evaluating the efficacy and safety of PT2977 in patients with VHL disease (who had at least 1 measurable RCC tumor; n=61). The subjects received 120 mg once daily doses. Study included ECG (12-lead, central lab) collections at screening, at pre-dose, 2 and 5 h post dose on Week 1 Day 1 and Week 3. Additional, pre-dose ECGs were collected on Weeks 5, 9, 13. Similarly, matching PK samples were collected at pre-dose, 2 and 5 h post dose on Week 1 Day 1 and Week 3. Additional, pre-dose PK samples were collected on Weeks 5, 9, 13. PK/ECG data up to 13 weeks of treatment were planned to use for primary QT assessment.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety, non-clinical overview (m2.4), and the previous IRT review under IND-132120 dated 02/14/2019 in DARRTS.

The in vitro activity of MK-6482 against the hERG potassium channel was assessed in a GLP electrophysiology study. MK-6482 exhibited no activity against hERG with an IC50 of >50 μM. This concentration of MK-6482 is > 26-fold higher than the mean unbound

Cmax value for the recommended clinical dose of 120 mg/day for treatment of cancer patients.

The cardiovascular system was assessed as part of the Good Laboratory Practice (GLP) 28-day and 13-week repeat-dose toxicity studies in dogs, which included hemodynamic (heart rate and blood pressure) and electrocardiographic parameters (PR interval, QRS duration, QT, and QTc intervals). In both studies, no effects on ECG parameters or blood pressure measurements were observed with MK-6482 treatment.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The largest upper bound of 90% CI of ΔQTcF for belzutifan 120 mg once daily was below 10 msec in the sponsor's by-time point analysis.

Reviewer's comment: The reviewer's independent by-time analysis results are similar to the sponsor's results. Please see Section 4.3 for details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTcF (i.e., >500 msec or >60 msec over baseline, HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment: The reviewer's independent categorical analysis results are similar to the sponsor's results. Please see Section 4.4 for details.

3.2.3 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between concentration of PT2977 (and PT3317) and ΔQTcF (change from baseline in QTcF) using a linear mixed-effects approach (Garnett et al. 2018) on all subjects in the analysis data set for cardiac assessment (up to 13 weeks of treatment).

The sponsor's final model suggested concentration-dependent increase in QT prolongation with the estimated population slope of the concentration-QTc relationship was 0.0053 ms per ng/mL (90% CI: 0.0033 to 0.0072). However, the results of the sponsor's analysis indicate that no large mean increases (i.e., >20 msec) in QTc interval was observed at the proposed therapeutic dose. The model predicted ΔQTcF (upper confidence interval) values of 2.55 (4.43) msec at the mean peak concentrations for the highest studied dose (120 mg once daily; geomean Cmax ~1390 ng/mL).

Reviewer's comment: Although there are numerical differences, the results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.

3.2.4 Safety Analysis

Overall, all (100%) participants experienced at least 1 AE, with 60 (98.4%) participants experiencing drug-related AEs and 15 (24.6%) participants experiencing an AE of CTCAE Grade 3 and above.

The most frequently reported AEs (reported in ≥10% of participants) include anemia (55 [90.2%] participants), fatigue (37 [60.7%]), headache (23 [37.7%]), dizziness (22 [36.1%]), nausea (19 [31.1%]), dyspnea (12 [19.7%]), arthralgia (11 [18%]), upper respiratory tract infection (11 [18%]), alanine aminotransferase increased (10 [16.4%]), myalgia (10 [16.4%]), vision blurred (9 [14.8%]), constipation (8 [13.1%]), hypertension (8 [13.1%]), abdominal pain (7 [11.5%]), aspartate aminotransferase increased (7 [11.5%]), and weight increased (7 [11.5%]).

The most frequently reported drug-related AEs with Grade ≥3 toxicity included anemia in 4 (6.6%) participants, fatigue in 3 (4.9%) participants, and hypoxia in 1 (1.6%) participant. Nine participants (14.8%) experienced SAEs and only 2 (3.3%) participants experienced SAEs assessed as drug-related (anemia and hypoxia).

One (1.6%) participant died in the study, due to and AE of acute fentanyl toxicity; this event was assessed as not drug-related.

AEs leading to treatment discontinuations were reported in 2 (3.3%) participants and in only 1 (1.6%) participant with dizziness was the event assessed as drug-related.

AEs leading to dose reduction were reported in 8 (13.1%) participants and were assessed as drug-related in 6 (9.8%) participants with fatigue being the most commonly reported event in 4 (6.6%) participants.

AEs leading to treatment interruption were reported in 24 (39.3%) participants, with events assessed as drug-related in 14 (23%) participants with fatigue being the most commonly reported event in 7 (11.5%) participants.

Most AES were Grade 1 to 2. There was 1 Grade 4 AE of retinal detachment and 1 Grade 5 AE of death from toxicity to various agents (acute fentanyl toxicity), both AEs assessed as not drug-related.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., significant ventricular arrhythmias or sudden cardiac death) occurred in this study. Within the SMQ "torsade de pointes/QT prolongation" the AEs of grade 2 syncope and grade 2 seizure were reported by 1 subject each and neither subject had QTc prolongation.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

The by-time analysis was based on ECG data collected up to Week 13 and included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer evaluated the ΔQTcF effect using descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for belzutifan 120 mg once daily. The maximum ΔQTcF values are shown in Table 2.

Figure 1: Mean and 90% CI of ΔQTcF Timecourse (unadjusted CIs).

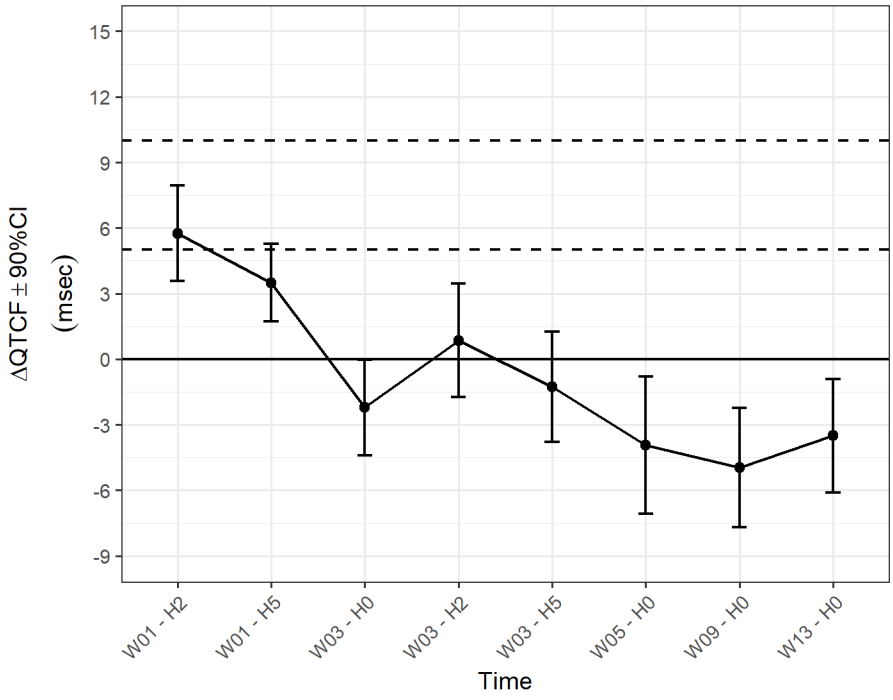


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Actual Treatment	WEEKC	N	Time (Hours)	ΔQTCF (msec)	90.0% CI (msec)
Belzutifan 120 mg QD	01	59	2.0	5.8	(3.6 to 7.9)
Belzutifan 120 mg QD	03	58	2.0	0.9	(-1.7 to 3.5)
Belzutifan 120 mg QD	05	61	0.0	-3.9	(-7.1 to -0.8)
Belzutifan 120 mg QD	09	56	0.0	-5.0	(-7.7 to -2.2)

Actual Treatment	WEEKC	N	Time (Hours)	ΔQTCF (msec)	90.0% CI (msec)
Belzutifan 120 mg QD	13	56	0.0	-3.5	(-6.1 to -0.9)

4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for belzutifan 120 mg once daily. The maximum ΔHR values are shown in Table 3.

Figure 2: Mean and 90% CI of ΔHR Timecourse

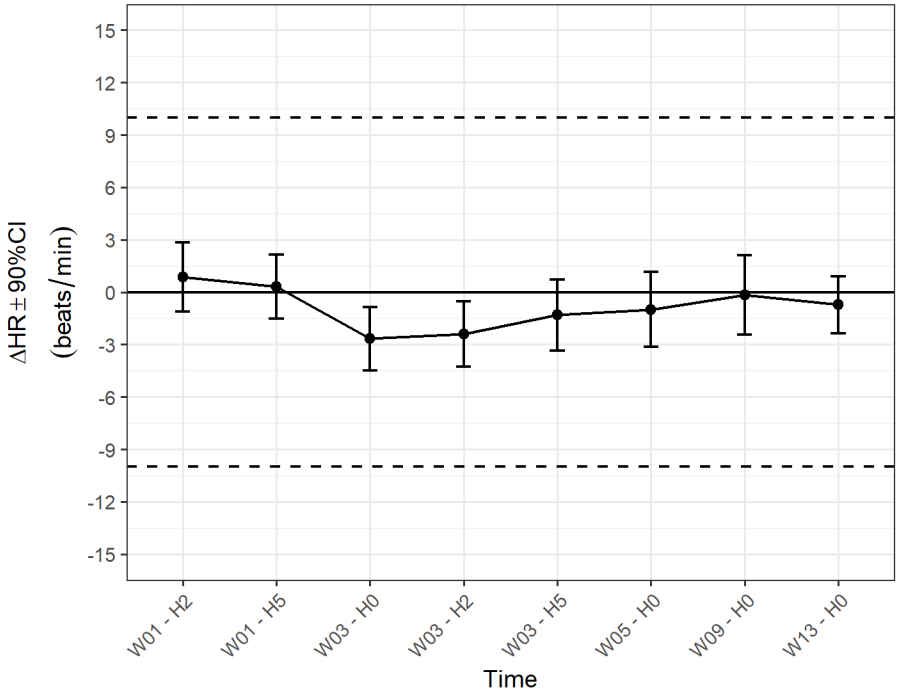


Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔHR

Actual Treatment	WEEKC	N	Time (Hours)	ΔHR (beats/min)	90.0% CI (beats/min)
Belzutifan 120 mg QD	01	59	2.0	0.9	(-1.1 to 2.8)
Belzutifan 120 mg QD	03	59	5.0	-1.3	(-3.4 to 0.7)
Belzutifan 120 mg QD	05	61	0.0	-1.0	(-3.1 to 1.1)
Belzutifan 120 mg QD	09	56	0.0	-0.2	(-2.4 to 2.1)
Belzutifan 120 mg QD	13	56	0.0	-0.7	(-2.4 to 0.9)

4.3.3 PR

Figure 3 displays the time profile of ΔPR for belzutifan 120 mg once daily. The maximum ΔPR values are shown in Table 4.

Figure 3: Mean and 90% CI of ΔPR Timecourse

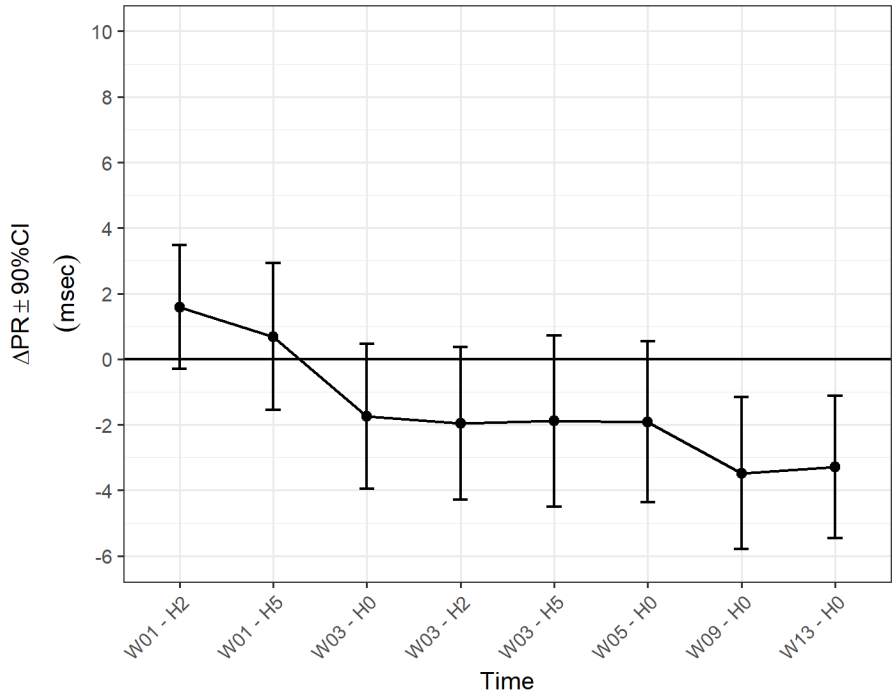


Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔPR

Actual Treatment	WEEKC	N	Time (Hours)	ΔPR (msec)	90.0% CI (msec)
Belzutifan 120 mg QD	01	58	2.0	1.6	(-0.3 to 3.5)
Belzutifan 120 mg QD	03	58	5.0	-1.9	(-4.5 to 0.7)
Belzutifan 120 mg QD	05	60	0.0	-1.9	(-4.4 to 0.5)
Belzutifan 120 mg QD	09	55	0.0	-3.5	(-5.8 to -1.2)
Belzutifan 120 mg QD	13	55	0.0	-3.3	(-5.5 to -1.1)

4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for belzutifan 120 mg once daily. The maximum ΔQRS values are shown in Table 5.

Figure 4: Mean and 90% CI of ΔQRS Timecourse

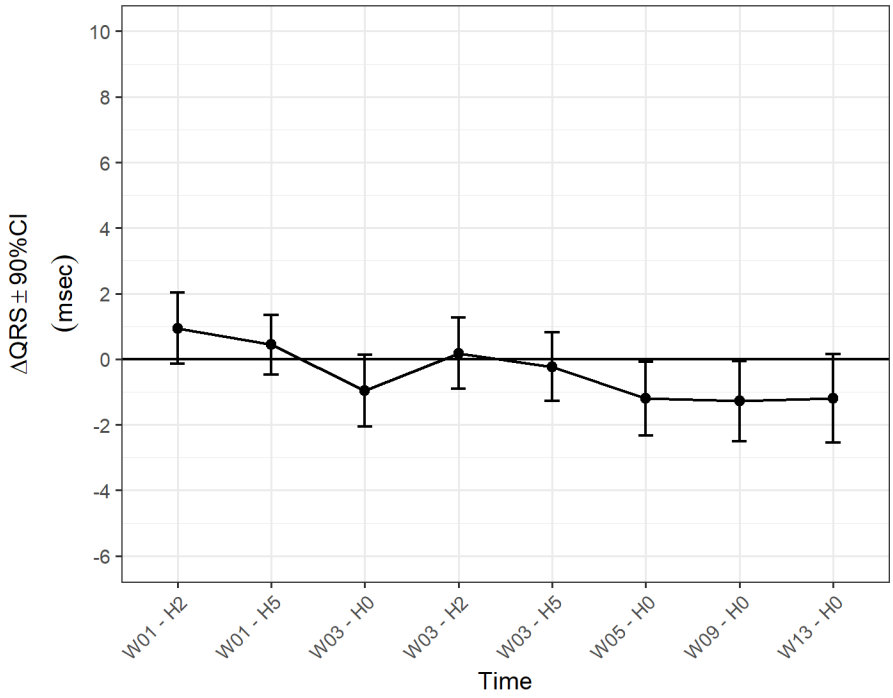


Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQRS

Actual Treatment	WEEKC	N	Time (Hours)	ΔQRS (msec)	90.0% CI (msec)
Belzutifan 120 mg QD	01	59	2.0	0.9	(-0.1 to 2.0)
Belzutifan 120 mg QD	03	58	2.0	0.2	(-0.9 to 1.3)
Belzutifan 120 mg QD	05	61	0.0	-1.2	(-2.3 to -0.1)
Belzutifan 120 mg QD	09	56	0.0	-1.3	(-2.5 to -0.1)
Belzutifan 120 mg QD	13	56	0.0	-1.2	(-2.5 to 0.2)

4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

Table 6 lists the number of subjects as well as the number of observations whose QTcF values were ≤450 msec and between 480 and 500 msec. There were no subjects who had QTcF between 450 and 480 msec or greater than 500 msec with a change from baseline greater than 25%.

Table 6: Categorical Analysis for QTcF (maximum)

	Total N		QTcF<=450 msec		480<QTcF<=500 msec	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	61	61	61 (100%)	61 (100%)	0 (0.0%)	0 (0.0%)
Belzutifan 120 mg QD	61	785	60 (98.4%)	779 (99.2%)	1 (1.6%)	2 (0.3%)

Table 7 lists the categorical analysis results for ΔQTcF (between 30 and 60 and greater than 60 msec).

Table 7: Categorical Analysis for ΔQTcF (maximum)

	Total N		30<ΔQTcF<=60 msec		ΔQTcF>60 msec	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Belzutifan 120 mg QD	61	785	4 (6.6%)	6 (0.8%)	1 (1.6%)	1 (0.1%)

4.4.2 HR

Table 8 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min).

Table 8: Categorical Analysis for HR (maximum)

	Total N		HR>100 beats/min		HR>100 beats/min & Increase >25%	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	61	61	0 (0.0%)	0 (0.0%)		
Belzutifan 120 mg QD	61	785	3 (4.9%)	4 (0.5%)	1 (1.6%)	2 (0.3%)

4.4.3 PR

No subject had PR >220 msec and with increase over baseline >25%.

4.4.4 QRS

No subjects had QRS >120 msec in the study.

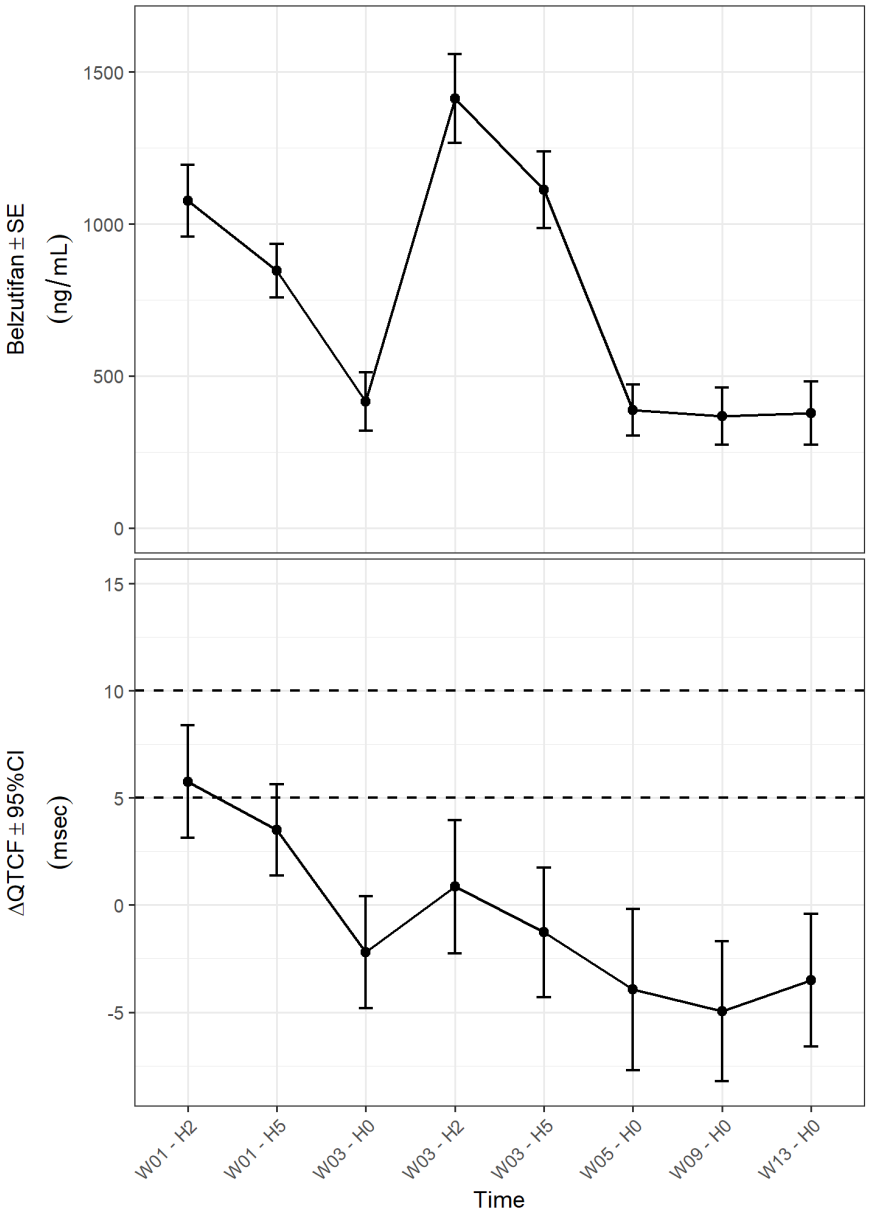
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of belzutifan (and its major metabolite) and ΔQTcF. Exposure response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK (up to 13 weeks of treatment; see Section 3.1.1).

Prior to evaluating the relationship between belzutifan (and its major metabolite) concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between belzutifan concentration and ΔQTc and 3) presence of non-linear relationship.

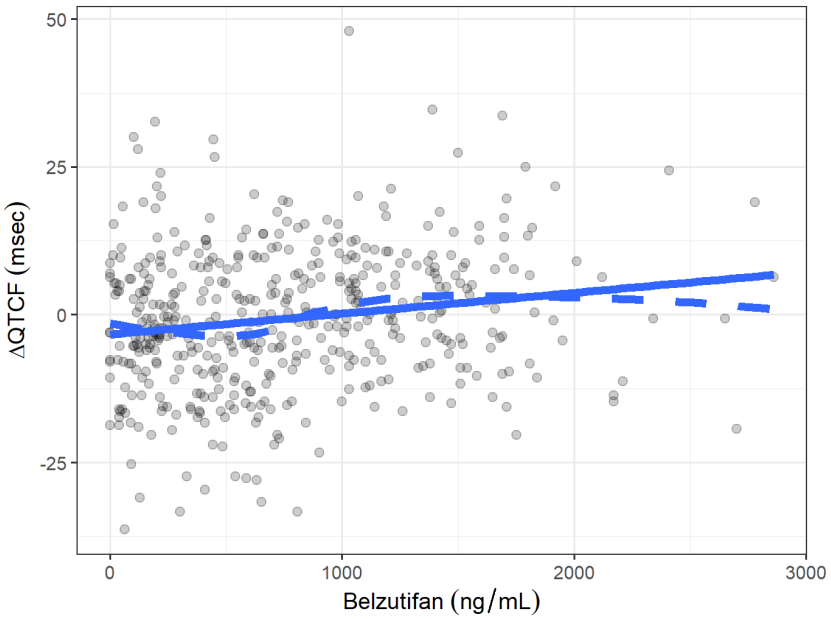
An evaluation of the time-course of belzutifan concentration and changes in ΔQTcF is shown in Figure 5. Although the intercept of the model was significant, there was no apparent correlation between the time at maximum effect on ΔQTcF and peak concentrations of belzutifan indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 8 bpm (Sections 4.3.2 and 4.4.2).

Figure 5: Time course of belzutifan concentration (top) and QTc (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between belzutifan concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between belzutifan concentration and ΔQTcF and supports the use of a linear model.

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Since the steady-state levels are expected to reach on week 3, the predicted effects at the concentrations of belzutifan on week 3 are presented in Table 1.

Figure 7: Goodness-of-fit plot for QTc

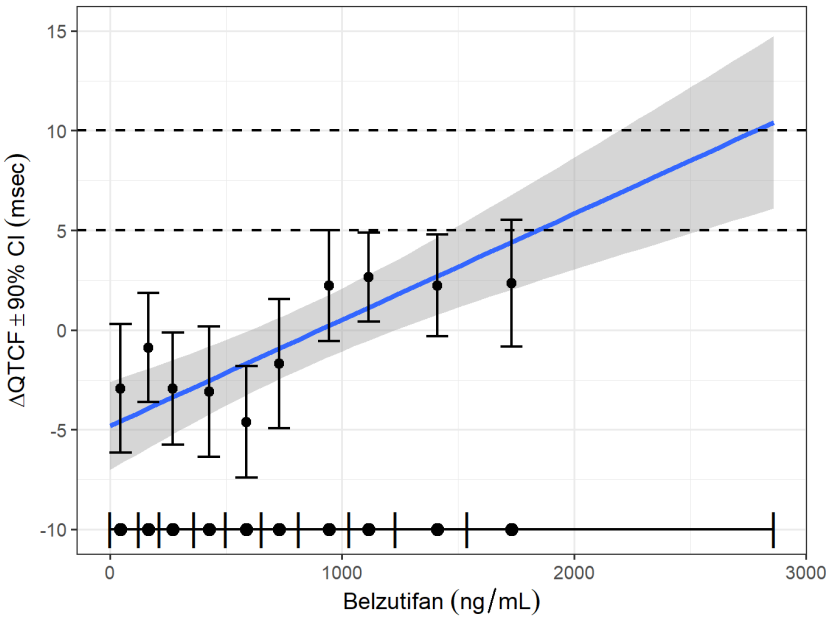


Table 9: Predictions from concentration-QTc model

Actual Treatment	Analysis Nominal Period Week (C)	Belzutifan (ng/mL)	ΔQTCF (msec)	90.0% CI (msec)
Belzutifan 120 mg QD	01	1009.7	0.6	(-1.0 to 2.2)
Belzutifan 120 mg QD	03	1313.3	2.2	(0.4 to 4.0)

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/s/

GIRISH K BENDE
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JANELL E CHEN
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Clinical Inspection Summary Report

Date	March 19, 2021
From	Yang-Min (Max) Ning, M.D., Ph.D. Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Jaleh Fallah, M.D. Michael Brave, M.D. Chana Weinstock, M.D., Team Leader Jeannette Dinin, Regulatory Project Manager Division of Oncology 1 (DO1) Office of Oncologic Diseases (OOD)
NDA #	215383
Applicant	Merck Sharp & Dohme Corp.
Drug	Belzutifan
NME (Yes/No)	Yes
Therapeutic Classification	Inhibitor of hypoxia-inducible factor (HIF) 2α
Proposed Indication	Treatment of von Hippel-Lindau disease-associated renal cell carcinoma, not requiring immediate surgery
Consultation Date	December 21, 2020
Review Priority	Priority
Summary Goal Date	March 26, 2021
Action Goal Date	April 16, 2021
PDUFA Date	September 15, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from an ongoing, single-arm Phase 2 study [MK-6482-004] were submitted to the Agency in support of this New Drug Application (NDA) for use of belzutifan in patients with von Hippel-Lindau disease-associated renal cell carcinoma who do not require immediate surgery. Three clinical investigators [Dr. Ramaprasad Srinivasan (Site 032), Dr. Eric Jonasch (Site 011), and Dr. Kimryn Rathmell (Site 015)] and the study sponsor Merck Sharp & Dohme Corporation were selected for clinical inspection.

The three investigator inspections confirmed that the submitted clinical data were verifiable with source records at the study sites, with no evidence of underreporting of adverse events. In general, based on the inspections of the three clinical investigators and the sponsor, the inspectional findings support validity of data as reported by the sponsor to the Agency. The clinical data generated by the three investigators appear to be reliable in support of this NDA for belzutifan.

II. BACKGROUND

Belzutifan is an inhibitor of hypoxia-inducible factor (HIF) 2α. The investigational name of belzutifan was MK-6482 [formerly PT2977] under IND 132120. The safety and efficacy of this product have been investigated in patients with von Hippel-Lindau (VHL) disease, a hereditary cancer syndrome which is associated with development of multiple tumors in affected individuals, including clear cell renal cell carcinomas (RCC) and other tumors in different organs. Besides surgical management of VHL-associated tumors, no systemic therapy has been approved to treat the disease or associated tumors.

For this NDA, the Applicant submitted clinical data from an ongoing Phase 2 study [MK-6482-004] and requested an accelerated approval of belzutifan for use in patients with VHL-associated RCC who do not require immediate surgery.

Study MK-6482-004 [NCT03401788] is an ongoing, single-arm trial of MK-6482 in subjects with VHL disease who had at least one measurable RCC not requiring immediate surgical intervention. Subjects with coexisting VHL-associated tumors [e.g., hemangioblastomas, pancreatic neuroendocrine tumor, etc.] in other organs were allowed. Evidence of tumor metastases at study entry, prior systematic anticancer treatments [e.g., anti-angiogenic therapy, investigational drugs including another HIF-2α inhibitor], and radiotherapy administered within 4 weeks prior to study entry were not allowed. The primary efficacy measure was overall response rate (ORR) as assessed by an independent review committee (IRC) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The ORR was defined as proportion of subjects who achieved a best confirmed complete response (CR) or partial response (PR) in VHL disease-associated RCC.

Subjects enrolled into the study were scheduled to receive MK-6482 orally at a dose of 120 mg once daily [three 40 mg tablets]. Study treatment were to be continued until disease progression, unacceptable toxicity, dosing interruption for more than 3 consecutive weeks due to a Grade 3 or 4 adverse event, consent withdrawal, loss to follow-up, or death.

Tumor assessments were to be performed with computed tomography (CT) or magnetic resonance imaging (MRI) scans at screening, within 7 days before Week 13 of study treatment, and then every 12 weeks thereafter. All CT and/or MRI scans were required to be submitted to the sponsor's contracted IRC [(b) (4)] for central review. Adverse events and abnormal laboratories were to be coded and graded for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

From 05/31/2018 through 06/01/2020 [data cutoff date for the current submission], the study enrolled 61 subjects from 11 study sites in four countries, including Denmark, France, the United Kingdom, and the United States (U.S.). Of those enrolled, 48 (79%) were from the U.S. All the 61 subjects received at least one dose of study treatment and were included in both efficacy and safety analyses for the current submission. The study was ongoing as of the

data cutoff date.

The Division of Oncology 1 (DO1) and OSI reviewed the submitted clinical site dataset and related investigator sites risk ranking and selected the above three investigators for inspection. These three investigators enrolled 44% of subjects in the study. In addition, the three investigator sites were associated with a high number of treatment responders and/or adverse events in the study. Given this application for a new class of agents targeting hypoxia-inducible factors, the sponsor inspection was also requested to evaluate its conduct and oversight of Study MK-6482-004.

III. RESULTS

1. Ramaprasad Srinivasan, M.D., Ph.D. (Site 032)
10 Center Drive
Bethesda, MD 20892-0001

Dr. Srinivasan was inspected on February 8-12, 2021, as a data audit for Study MK-6482-004. This was the first FDA inspection for this investigator. The site screened 14 subjects and enrolled 13 of them into the study. As of the data cutoff, one subject [# (b) (6)] was discontinued from study treatment secondary to consent withdrawal and the rest of subjects remained on study treatment. At the time of the inspection, two additional subjects [# (b) (6) and (b) (6)] were found to have discontinued study treatment due to disease progression or consent withdrawal, which occurred after the data cutoff date.

All subject source records were reviewed during the inspection and were compared with the submitted data listings for the site. The reviewed records included but were not limited to the informed consents, eligibility criteria, enrollment log, scans performed and related local documentation for efficacy assessments [e.g., Tumor Measurements RECIST Criteria] and submissions for central review, adverse events/serious adverse events, laboratory results, ophthalmology reports, concomitant medications, protocol deviations, electronic case report forms (eCRF), and investigational drug accountability logs. The reviewed regulatory documents and procedures included the study protocol and amendments, Institutional Review Board (IRB) approvals and continuing reviews, investigators' signed Form FDA 1572s, financial disclosures, Delegation of Authority, training records, access to the eCRF system and completion of eCRFs, reporting to the sponsor, study monitoring records, and control of the study product MK-6482 at the site.

The inspection found no significant regulatory violations. All the 13 enrolled subjects met the eligibility criteria and had their informed consent documentation at the site. For these subjects, the submitted data listings were verifiable with source records at the site. Note that the Applicant's reported best tumor response information by the IRC was not available to the study site.

At the conclusion of this inspection, no Form FDA 483, Inspectional Observations, was issued to Dr. Srinivasan.

2. Eric Jonasch, M.D. (Site 011)
1220 Holcombe Blvd, Unit 1274
Houston, TX 77030

Dr. Jonasch was inspected from February 24 through March 5, 2021, as a data audit for Study MK-6482-004. This was the first FDA inspection of this investigator. The study site enrolled 9 subjects into the study. One subject [# (b) (6)] was transferred to another study site [Site 048] in the United Kingdom (U.K.) (b) (6) during the study. Of the 8 remaining subjects, two were discontinued due to consent withdrawal [Subject # (b) (6)] or death [Subject # (b) (6)] which was reported to be unrelated to study treatment. As of the data cutoff, 6 subjects continued receiving study treatment.

Source records for all the 9 subjects were reviewed and compared with the submitted data listings for the site. Note that data listings for the subject transferred to the U.K. were included for Site 048 instead for this site. The reviewed records included the informed consents, case history, efficacy endpoint-related measurements, adverse event reporting, concomitant medications, protocol and amendments, signed Statement of Investigator, financial disclosure statements, IRB submissions and correspondence, test article accountability, and sponsor monitoring activities.

The inspection found that the submitted data listings for each subject were verifiable with source records at the site, including scan reports, RECIST measurement documentation, adverse events, and laboratory tests. There were no discrepancies noted.

The inspection also identified deficiencies in the contemporaneousness of source data documentation at the site, which led to a Form FDA 483 issued to the investigator, citing "Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent". Specifically, some electronic source data documented at the site cannot be verified for accuracy in date or for the protocol-required birth control methods. This observation included: 1) for Subject # (b) (6), the informed consent documentation dated 04/23/2018 was not entered into the site's electronic medical record (EMR) until 05/16/2018, but the entry date was backdated to 04/23/2018; for the same subject, the Study Entrance (Inclusion/Exclusion Criteria) dated 06/27/2018 was not entered into the EMR until 07/05/2018 and was also backdated to 06/27/2018 as Study Day 1. Similar delayed data entries to the EMR and backdating were also found for Subjects # (b) (6)) for all the subjects audited, there was no documentation of birth control methods discussed, planned, or used for this study. The investigator acknowledged the issued FDA 483 and committed to providing a written response within 15 business days.

Reviewer's Comments: This inspection verified the submitted data from this investigator against the reviewed source records. As of March 19, 2021, OSI has not received a written response from the investigator to address the inspectional observations. Although the above-described regulatory violations were noted, these findings do not appear to affect the validity of the submitted data or subject protection at the site.

3. Kimryn Rathmell (Site 015)
2220 Pierce Avenue
Nashville, TN 37232

Dr. Rathmell was inspected on March 1-4, 2021, as a data audit for Study MK-6482-004. For the investigator, this was the initial FDA inspection. Currently, the inspection report is not available, and the following information on Dr. Rathmell's conduct of this study is based on the preliminary summary from the field inspector.

The site enrolled 6 subjects into the study. All the 6 subjects received study treatment. As of the data cutoff date, all the subjects remained on study treatment. The study was active at the time of the inspection.

The inspection reviewed source records for all the 6 subjects as well as related regulatory documents, including the informed consents, clinical records, subject eligibility, case report forms, efficacy endpoint assessments and local RECIST documentation, adverse events, drug accountability, and monitoring procedures.

The inspection identified no regulatory violations. The Applicant's submitted data for this site were verifiable with source records at the site. The protocol-required scans were performed as scheduled and all the scans were uploaded to the IRC (b) (4) There was no evidence of underreporting of adverse events. At the closeout of this inspection, no Form FDA 483 was issued to Dr. Rathmell.

***Reviewer's Comments**: An amendment to this clinical inspection summary will be introduced if the inspection report for Dr. Rathmell contains substantial differences to alter the current assessment or compliance conclusion.*

4. Merck Sharp & Dohme Corporation (Study Sponsor)
126 E Lincoln Avenue
Rahway, NJ 07065-4607

The study sponsor was inspected between January 11-20, 2021, to evaluate its conduct, oversight, and management of Study MK-6482-004. For this study sponsor, there were multiple FDA inspections in recent years, with the last one conducted from 08/26/2019 through 09/06/2019.

The current inspection included a comprehensive review of sponsor's records pertinent to Study MK-6482-004. The reviewed records involved but were not limited to the sponsor's history and organizational charts, key individuals' responsibility, standard operating procedures, selection of the contract research organizations (CRO) that participated in the study and their service agreements, selection and qualification of study monitors and clinical investigators, signed Form FDA 1572s and financial disclosures, study-related training, study protocol development and study continuation from the former sponsor Peloton Therapeutics Inc., to the current sponsor following acquisition in 2019, study monitoring plans, adverse event reporting, test article accountability records, corrective and preventative action plans, and relevant meeting minutes. The inspection also focused on examining documents related to sponsor's contracted the IRC (b) (4) , including the initial contract, data transfer plans, data transfer process and post-transfer validation.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued to the sponsor for "Failure to ensure proper monitoring of the study". Specifically, the inspection found delays in the submission of site monitoring visit follow-up letters from study sites within 20 business days of the visit. The Clinical Monitoring Plan (CMP) stated, "Site visit follow-up letters should be submitted with the visit report within 20 business days of the visit"; whereas for Site 011, the sponsor failed to ensure that 11 out of 22 monitoring follow-up letters were submitted within the specified 20 business days of visit; and for Site 040, 9 out of 21 monitoring follow-up letters were not submitted with the visit reports within the specified 20 business days of the visit. The sponsor acknowledged the observation and submitted a written response on 01/28/2021. To address this observation, the sponsor had completed re-training of all assigned research associates on the CMP timelines and tracked follow-up letter submission dates to adhere to the CMP-required 20 days following visit. The sponsor committed to implementing the tracking plan from 03/15/2021 through the end of this study.

Besides the above observation, the inspection did not find additional significant regulatory violations in the sponsor's conduct and management of Study MK-6482-004. The inspection revealed adequate adherence to the regulations and the investigational plan. Of note, the sponsor's designated CRO (b) (4), which performed the data management and biostatistical analysis for this study, processed the data transfer from the IRC [(b) (4)] in July 2020 and had read-only access to the IRC data.

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cc:

Central Documentation
Review Division /Division Director
Review Division/Medical Officer
Review Division /Medical Team Leader
Review Division /Project Manager
OSI/Office Director
OSI/DCCE/ Division Director
OSI/DCCE/GCPAB Chief
OSI/DCCE/GCPAB Team Leader
OSI/ GCP Program Analysts
OSI/Database Project Manager

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Medical Officer's Review of NDA 215383
Ophthalmology Consultant

NDA 215383 Submission: 12/15/2020
Review completed: 3/ 3/2021

Name: Belzutifan

Sponsor: Merck Sharp & Dohme Corp

Pharmacologic Category: Inhibitor of HIF-2α,

Indications: Treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery.

Requested: We have received waive 1 of an RTOR submission for the NME and first in class HIF2 alpha inhibitor belzutifan, NDA 215383, which includes the safety and efficacy data for the proposed indication: "Treatment of patients with Von Hippel-Lindau disease (VHL)-associated renal cell carcinoma (RCC)". The full submission will be here on January 15th, 2021. There is no currently-approved drugs for the proposed indication, although TKIs can be used off-label. However, this drug appears to have a more tolerable safety profile for long-term use as would be the case for these patients. The sponsor has not submitted their proposed labeling yet. However, the efficacy data in VHL disease-associated non-RCC tumors seems impressive, particularly for CNS hemangioblastoma, retinal angiomas, and benign pancreatic neoplasms. In many cases these tumors may leave patients with significant morbidities such as blindness and neurological defects. We are requesting consult opinion from the neuro-oncology, ophthalmology and GI oncology teams to assess the safety and efficacy of this drug in comparison with currently available treatment options for these non-RCC tumors, especially regarding including some of these data in product labeling. "

Reviewer's Comments: *Comments in this review are limited to areas of ophthalmologic interest.*

Background: Von Hippel-Lindau (VHL) disease is a hereditary cancer syndrome transmitted in an autosomal dominant fashion and is characterized by a germline mutation/deletion of the VHL gene. Affected individuals are at risk for developing tumors (both cancerous and noncancerous) and fluid-filled sacs (cysts) in a number of organs, such as renal cysts and renal tumors (ccRCC histological subtype), pancreatic cysts, pancreatic neuroendocrine tumors, pheochromocytomas, hemangioblastomas of the brain and spinal cord, retinal angiomas, inner ear endolymphatic sac tumors, and epididymal and broad ligament cystadenomas. RCC occurs in up to 70% of individuals with VHL disease and is a leading cause of mortality. Approximately one third of patients who have VHL disease (13–42%) die of metastatic RCC disease. The first manifestations of VHL disease may appear during young adulthood; however, the signs and symptoms of VHL disease can occur throughout life.

PROTOCOL TITLE: An Open-label Phase 2 Study to Evaluate PT2977 for the Treatment of von Hippel-Lindau Disease-associated Renal Cell Carcinoma

STUDY IDENTIFIERS:
IND: 137354 NCT: 03401788

STUDY PHASE: 2

INDICATION: Participants with von Hippel-Lindau (VHL) Disease-associated Renal Cell Carcinoma (RCC)

STUDY CENTERS: 11 centers in 4 countries; 67 participants screened, 61 participants received study intervention.

STUDY STATUS: This study is ongoing; this report is based on the data cutoff (DCO) date of 01-JUN-2020.

First Patient, First Visit Last Patient, Last Visit Data Cut-off 31-MAY-2018 N/A 01-JUN-2020

METHODOLOGY: Ongoing, open-label, multicenter, Phase 2 study to evaluate the efficacy and safety of MK-6482 as treatment for participants with VHL disease who had at least 1 measurable RCC tumor. Participants may have also had VHL disease-associated tumors in other organ systems at screening which could have been measurable and/or non-measurable lesions. Participants were evaluated with imaging every 12 weeks in only those areas of VHL disease present at screening as determined by investigator to assess response to treatment. Measurements of VHL-associated RCC target lesions at 2 timepoints prior to the screening imaging were collected to determine the tumor growth rate before treatment with MK-6482. All images obtained were submitted to an independent review committee (IRC) to assess objective response and progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Radiographic response assessments were made separately for each VHL-associated organ system using RECIST 1.1, e.g., RCC, pancreas lesions, and CNS hemangioblastomas. Retinal angiomas were assessed by an independent central committee of ophthalmologists, reviewing fundoscopic images.

Reviewer's Comments: *Neither the fundoscopic images nor the report prepared by the independent central committee of ophthalmologists who reviewed the fundoscopic images has been submitted to the NDA.*

STUDY RESULTS:
Number of participants treated/ongoing/discontinued: 61 participants received at least one dose of study treatment. As of the DCO, 5 (8.2%) participants had discontinued study treatment and 3 (4.9%) participants had withdrawn from the study.

Overall Median Age (range): 41 years (19 to 66 years)

Gender: 32 (52.5%) male, 29 (47.5%) female
Ethnicity: 54 (88.5%) not Hispanic or Latino, 6 (9.8%) Hispanic or Latino, 1 (1.6%) unknown

Race: 55 (90.2%) white, 2 (3.3%) black or African-American, 1 (1.6%) Asian, 1 (1.6%) native Hawaiian or other Pacific islander, 2 (3.3%) unknown

Distribution of abnormalities: Based on investigator's assessment, 51 (83.6%) participants had CNS hemangioblastomas, 31 (50.8%) had pancreatic lesions, 17 (27.9%) had retinal lesions, 10 (16.4%) had epididymal cystadenomas, 3 (4.9%) had adrenal lesions, 2 (3.3%) had other lesions (not specified), and 1 (1.6%) had endolymphatic sac tumors.

Reviewer's Comments: *Retinal capillary hemangioma (RCH) is a frequent and early manifestation of VHL disease. RCH usually occurs in more than half of individuals with VHL.[1] In this study, only 28% had retinal lesions.*

11.1.3.6 Retinal Lesions Retinal hemangioblastoma response, per IRC, was assessed using various parameters such as number/size/location, degree of feeder/drainer engorgement (mild/prominent), presence of intraretinal heme, presence of preretinal heme, presence of vitreous heme, presence of lipid exudation, presence of subretinal fluid, and presence of fibrosis. Details of the IRC charter and associated documents are available upon request.

Reviewer's Comments: *The IRC charter and associated documents should be requested.*

Similarly to CNS hemangioblastomas, it was decided to pursue IRC review of retinal lesions after study enrollment was completed. IRC assessment was therefore limited to those participants who investigators had originally assessed as having retinal hemangioblastomas at screening and were thus followed every 12 weeks with fundus photography. Those participants who, per investigator assessment, were considered as not having retinal lesions at baseline did not have follow-up fundus photography imaging.

Sixteen of 17 participants with baseline retinal hemangioblastomas were evaluable for response with follow-up evaluations. Responses were measured at eye level. The best overall response at the participant level was based on the following assessment: the participant was improved if 1 eye was improved; the participant was progressed if 1 eye was progressed (regardless of the status of the other eye); the participant was stable if both eyes were stable. Responses needed to be confirmed at a subsequent timepoint.

An improvement of retinal lesions was observed after treatment with MK-6482. Of 29 total eyes with retinal hemangioblastomas, 55.2% improved and 41.4% were stable as of the DCO. Of 16 evaluable participants with retinal hemangioblastomas, 11 participants (68.8%) improved. All 11 participants had an improvement for ≥6 months, and of these, 2 participants had improvement for ≥9 months.

At Week 49, as per investigator's assessment, 61.3% of the participants with retinal hemangioblastomas had improved compared with baseline and 38.7% were stable compared with baseline. No participants with retinal lesions underwent surgeries as of the DCO.

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[1] Singh AD, Shields CL, Shields JA. von Hippel-Lindau Disease. *Survey of Ophthalmology*. 2001; 46(2):117-142.

Pt ID	Laterality	No Image	# Lesions	Laser Tx	Fibrosis	Scarring	Improved	Initial VA	Final VA
(b) (6)	R		1	x	x	x	X	25	20
	R		1	x	x		X	20	20
	L		1	x	x		X	20	20
	R		4	x	x		X	50	125
	R		1	x			X	16	25
	L		2	x			X	32	32
	L		4	x			X	25	25
	R		2		x		X	20	25
	R		2		x		X	50	32
	R		1				X	20	16
	L		1				X	32	12.5
	R		2				X	25	16
	L		2				X	50	25
	R		2				X	25	
	R		3				X	NLP	NLP
	L		0		x	x		100	150
	L		0					20	25
	L		0					20	20
	L		0					32	25
	L		0					20	20
	R		0					25	25
	L		0					20	20
	R		0					30	50
	L		0					70	50
	R		0					20	20
	L		0					20	20
	L		0					25	
	L		0					25	125
	R	x						LP	LP
	R	x						20	13
	L	x						20	25
	R	x						ND	ND

Reviewer's Comments: *Disagree with the characterization of improvement. Of the 16 subjects (32 eyes) theoretically available for retinal evaluation, three (3) did not have any images in one or both eyes. Of the 28 eyes with images, 13 eyes did not have any lesions at baseline. Of the 15 eyes remaining, one (1) eye had no light perception (completely blind) at baseline, seven (7) had laser treatment potentially resulting in lesion improvement and two (2) without laser treatment were already showing fibrosis, a stage of improvement. The remaining 5 eyes (16%) of the eyes followed in this trial appeared to have improvement without potentially confounding circumstances.*

Summary/Requests for Information:

1. Only 5 eyes (4 subjects) demonstrated improvement in retinal lesions without potentially confounding circumstances. The majority of eyes reported as stable or improved in the trial did not have any lesions at baseline.

2. Patient (b) (6) is reported as having a retinal detachment. The eye with the retinal detachment has not been identified. The investigator classified the event as not related to treatment and related to pre-existing lesions related to Von Hippel-Lindau disease; however, one of the eyes did not have any evidence of retinal disease. Even for eyes with retinal lesions, all retinal lesions do not lead to retinal detachments. Retinal detachments were not listed in the Investigator Brochure as a potential consequence of retinal lesions. Both eyes of this subject lost visual acuity. The eye with the retinal detachment should be identified and an explanation provided of why this retinal detachment should not be classified as drug related.

3. Patient (b) (6) is reported as having a retinal vein occlusion. Retinal vein occlusions are potentially sight threatening. An explain should be provided why this event is listed as a Grade 2 event and why it is not listed as drug related.

4. Study MK-6482-004 is reported as having 28% of patients with retinal hemangioblastomas at screening. The IRC assessment of retinal hemangioblastomas was limited to those participants for whom investigators had originally assessed as having retinal hemangioblastomas at screening. The Von Hippel-Lindau Natural History Study, Epidemiology No. EP05047.001, VEAP #: 9038 reports retinal hemangioblastomas in twice as many patients (57%). An included reference article, Survey of Ophthalmology, Volume 46(2), Sept-Oct 2001, reports a frequency of retinal hemangioblastomas of 50-60%. An explanation should be provided whether there is a likely reason why the population studied in MK-6482-004 does not appear to be representative of the typical Von Hippel-Lindau population.

5. Retinal angiomas were assessed by an independent central committee of ophthalmologists, reviewing fundoscopic images. A copy of the fundoscopic images that were assessed and a copy of all reports by the independent central committee of ophthalmologists should be submitted to the NDA.

Wiley A. Chambers, M.D.
Supervisory Physician, Ophthalmology

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/s/

WILEY A CHAMBERS
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